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# American Journal of Obstetrics and Gynecology

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## Original Communications

### THE CAUSES OF FETAL AND NEONATAL MORTALITY\*

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THE study of the causes of fetal mortality should be an increasingly important problem, for only in this way will it be possible to devise methods which will offer sufficient safety to the child to give us courage to avoid the tempting but less safe cesarean section.

With an ever-increasing emphasis on the importance of delivering a normal healthy child for each planned pregnancy, the obstetrician frequently finds himself in the position of recommending cesarean section on purely fetal indications. While this method of delivery usually offers the easiest way out of a difficult situation and frequently improves the chances of fetal survival, we cannot overlook the discomfoting fact that the risk to the mother is much greater under these circumstances than when the delivery is effected through the vagina. It seems logical, therefore, to increase our efforts in the study of the causes of fetal deaths, with the hopeful outlook that the pelvic delivery, which unquestionably offers maximum safety to the mother, may be made increasingly safe for the child. Only in this way will it be possible further to lower *both* the fetal and maternal mortality. A high fetal mortality rate cannot be

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NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

combated entirely with a high cesarean section rate, for it may be shown readily from our figures that, even if a cesarean section were done in every patient that came to the labor room, there still would be a minimum fetal loss of 2.3 per cent, due to causes which are in no way related to the accidents of labor and which could not be prevented by the operation. Obviously then, an increasing cesarean section rate will have the effect of giving diminishing returns in terms of live births while the maternal mortality would unquestionably rise sharply or, to put it in another way, an increasing cesarean section rate reaches a point where it costs too many mothers for the prospect of saving a proportionately smaller number of babies.

It was with these general ideas in mind that this study was contemplated. It represents a critical clinical and pathologic review of 1,000 consecutive fetal deaths occurring at the New York Lying-in Hospital and the Sloane Hospital for Women. The study covers a period of six years from 1935 to 1940, inclusive. The data from both services have been combined and presented in that form.

There are no striking differences in the nature of the material handled, the organization of staffs, or the physical equipment of these services. In most respects, the figures obtained were entirely comparable and seem suitable to present in a combined form.

Among the 1,000 deaths reviewed, only 16 occurred among unregistered cases. There was a combined autopsy rate of 89.3 per cent. Thus it is seen that in the vast majority of cases there were both complete clinical and pathologic data available for study.

Notwithstanding such complete clinical and anatomic data, it is not always a simple matter to evaluate the factors that are concerned with a fetal death. Even when the anatomic findings of a carefully performed post-mortem examination are known and these are correlated with the events which occurred during labor, it may be difficult to classify the death with certainty. The multiplicity of factors involved in a single case and the various degrees of emphasis placed upon them may lead different observers to reach different conclusions in ascribing primary and secondary causes of death. A good example is the frequently seen premature baby weighing about 2,000 Gm. with a small amount of subdural hemorrhage. The difficulty of ascribing primary and secondary causes of death in such a case becomes obvious at once. If the weight of the fetus were changed from 2,000 Gm. to 1,000 Gm., then prematurity as the primary cause with birth trauma as a secondary cause would be in more general agreement. There are other factors which make for difficulty. These involve the actual interpretation of post-mortem findings. Neonatal pathology in many instances lacks the confirmatory data of the experimental pathologist, so that the inter-

pretation of the lesions we see are not always clear. To mention one such lesion we may refer again to the intracranial hemorrhages found in the premature infant. Frequently these occur as small subarachnoid or intraventricular hemorrhages with no evidence of injury to the dural supporting system, while the lungs, pleura, pericardium, thymus, adrenals, and other viscera show the ruptured capillaries so characteristic of asphyxia. In such a case, it is a matter of individual interpretation to ascribe the intracranial findings either to birth injury on the one hand or to asphyxia on the other. What is the significance of hemorrhage into the lung? Is it related to the hemorrhagic lesions of the newborn or does it represent evidence of intrauterine asphyxia? What is the significance of masses of amniotic cells in the lungs? Are they evidence of asphyxia followed by aspiration of amniotic fluid and cells or is their presence physiologic, as a part of the so-called tidal flow of amniotic fluid? What is the relationship of congenital pneumonia to asphyxia? Does pneumonia follow after asphyxia, which causes the child to aspirate large quantities of bacteria and pus cells from an infected amniotic sac, or do these organisms gain access to the lungs by some other mechanism? It is obvious, therefore, that, while in a majority of cases the primary cause of death may be ascribed with certainty, there are a considerable number in which the final classification becomes an opinion based on all the clinical and anatomic facts available and its accuracy depends largely upon the completeness of these facts and the judgment and clinical-pathologic experience of the observer.

At the very beginning of the study we found it necessary to reach some agreement on the classification of the premature infant, because the respective institutions followed different practices in this respect. Hence, we reclassified all the fetal deaths according to the classification of Scammon (Table I).

TABLE I

Previaible prematures	92
(Must satisfy any two of the following criteria)	
From 500 to 999 Gm. in weight	
From 28 to 35 cm. in length	
From 22nd to 28th week	
Viable prematures	350
(Must satisfy any two of the following criteria)	
From 1,000 to 2,499 Gm. in weight	
From 35.1 to 47 cm. in length	
From 29th to end of 37th week	
Term	558
Total	1,000
Total deliveries	25,823
Total fetal and neonatal deaths	1,000
Gross fetal and neonatal mortality rate	3.87 per cent
Fetal and neonatal mortality rate exclusive of previaible prematures	3.52 per cent

Some question might be raised about the inclusion of the previable premature infants in this study, since the mortality rate in this group is very nearly 100 per cent. There are several reasons why it seems desirable to include them in any study of stillbirths. First, these tiny babies occasionally live, and for this reason we should attempt to discover the causes of death in the others with the hope that more and more of them may be salvaged. Second, these infants may be studied by routine pathologic methods. To consider them as abortions rather than stillbirths tends toward their disposal along with other abortions in which routine pathologic techniques are not applicable. In the third place, they are frequently associated with maternal disease which necessitates an interruption of pregnancy. By adding them to the total group we obtain a more complete picture of the relationship of maternal disease to fetal deaths.

In Table I we note that there were 25,823 deliveries at both hospitals during the period covered by this study, resulting in a gross fetal mortality rate of 3.87 per cent. If the previable prematures are excluded, the rate becomes 3.52 per cent. On the basis of live births the rates are 4.03 per cent if the previable prematures are included and 3.66 per cent when they are excluded. The premature infants account for 44.2 per cent of the total number of deaths.

The causes of death in the entire group are shown in Table II.

TABLE II. DISTRIBUTION OF CAUSES IN 1,000 CASES OF FETAL AND NEONATAL DEATHS

CAUSES	NUMBER OF CASES
Asphyxia	198
Prematurity (primary)	185
Congenital abnormalities	141
Maceration, cause unknown	130
Birth injury	115
Congenital pneumonia	58
Maceration and toxemia	52
None	30
Erythroblastosis	28
Hemorrhagic disease of newborn	21
Septicemia	18
Congenital syphilis	6
Maceration and diabetes	5
Diarrhea newborn	4
Aspiration of food	3
Perforated ulcer ileum	1
Gangrene of colon	1
Intestinal obstruction	1
Multiple abscesses of liver	1
Adrenal hemorrhage	1
Toxoplasmosis	1

Attention is called to the fact that these are listed as primary causes only. While it is obvious that in many instances there were multiple

causes of death, it seemed that a grouping according to combinations of primary and secondary causes would be cumbersome to the point of being valueless. Each case was carefully studied from both a clinical and a pathologic viewpoint, as previously stated, and an attempt was made to ascertain the most important cause of death.

Prematurity appears as the cause of death in 185 cases while Table I shows that 442 cases were classified in the premature group. The difference between these two figures (257), therefore represents the number of premature infants that died of causes that were more significant than their premature state and for that reason were classified under those causes. It follows, then, that a relatively large number of premature infants might have lived if they had not been the victims of some other pathologic conditions.

It is noteworthy that of the causes of death those which are more directly related to labor, namely: asphyxia (19.8 per cent), birth injury (11.5 per cent), and pneumonia (5.8 per cent), appear in that order.

A relatively large number of deaths (13 per cent) occurred before the onset of labor without known cause. These fetuses were born in a macerated state, and in the absence of any known cause are a distinct challenge to the research worker in this field. Our knowledge about this group is limited because the poor state of preservation of all cell structure makes post-mortem studies valueless. It will be of interest to follow the work that is being done with the Rh factor to see if deaths of this nature may be explained on that basis.

TABLE III. RELATIONSHIP OF RACE TO FETAL AND NEONATAL MORTALITY

	TOTAL NO. DELIVERED	NO. OF DEATHS	PERCENTAGE RATE
White	23,729	868	3.65
Negro	2,094	132	6.30

TABLE III, A. CAUSES OF DEATH AMONG WHITES AND NEGROES

CAUSES	INCIDENCE AMONG TOTAL WHITES (PER CENT)	INCIDENCE AMONG TOTAL NEGROES (PER CENT)
Asphyxia	19.0	25.0
Prematurity	17.7	23.5
Congenital malformations	14.7	9.8
Maceration, cause unknown	13.6	9.0
Birth injury	11.7	9.8
Maceration, due to toxemia	4.9	6.8
Erythroblastosis	3.1	0.8
Hemorrhagic disease of newborn	1.9	3.0

TABLE IV. RELATIONSHIP OF PARITY TO FETAL AND NEONATAL MORTALITY

	TOTAL NO. DELIVERED	TOTAL NO. OF DEATHS	MORTALITY RATE
Primiparas	13,241	509	3.84
Multiparas	12,582	491	3.90



Maternal disease directly accounted for 6.3 per cent of all fetal deaths. This figure, however, does not completely express the importance of maternal disease in the problem since, in at least an additional 55 cases, maternal disease was indirectly responsible for a premature labor which in turn resulted in a stillbirth or neonatal death. It may be stated, therefore, that 11.8 per cent of the fetal deaths were directly or indirectly the result of maternal disease. Congenital syphilis accounted for only 0.6 per cent of the deaths. This figure is in marked contrast to those found in older reports when syphilis was among the most important causes.

The fetal mortality rate among the whites and Negroes as noted in Table III shows a definitely higher rate among the latter. The causes

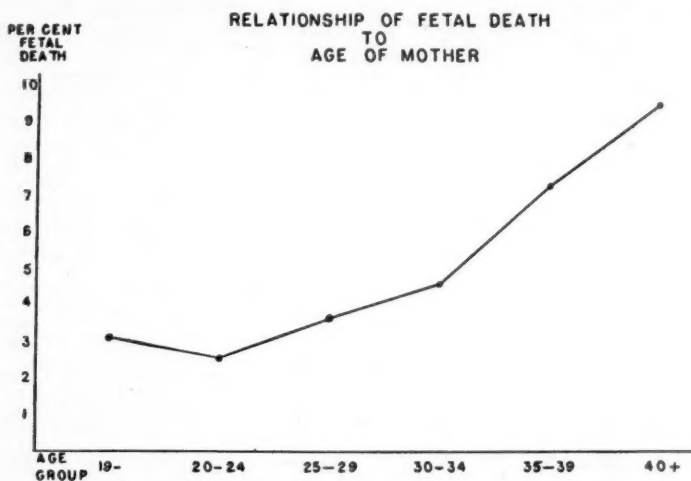


Fig. 1.

of death were studied separately and those conditions which showed differences of more than 1 per cent are recorded in Table IIIA. The higher fetal mortality rate among the Negroes was due mainly to a higher incidence of prematurity and asphyxia. They also showed a slightly higher incidence of deaths due to toxemia and hemorrhagic disease of the newborn. Among the whites, on the other hand, there was a greater fetal death rate due to congenital malformations, maceration of unknown cause and erythroblastosis.

It was of interest to note (Table IV) that the fetal death rate among multiparas and primiparas is practically identical. Apparently the larger number of deaths due to dystocia among primiparas is completely balanced in the multiparas by the higher incidence of deaths due to the accidents of labor.

The relationship of the age of the patient to the proportion of living and dead infants delivered at each age level is shown graphically in Fig. 1, from which we may conclude that the incidence of fetal deaths was lowest among the women between 20 and 24 years of age and highest in women that were 40 years old or over. There is a gradual rise in fetal mortality rate as the woman advances beyond age 30, in spite of the greater latitude in operative interference aimed toward saving the fetus in these cases.

We next studied the relationship of the duration of labor to fetal mortality (Table V) and noted that labors under three hours and those

TABLE V. RELATIONSHIP OF THE DURATION OF LABOR TO FETAL AND NEONATAL MORTALITY

	LESS THAN 3 HOURS	3-5	6-11	12-17	18-23	24-29	MORE THAN 30 HOURS
Total No. delivered	1,216	4,182	7,993	5,136	2,774	1,115	2,062
No. of deaths	81	140	237	170	82	55	181
Percentage rate	6.66	3.34	2.96	3.40	2.95	3.88	8.77

that exceed thirty hours show distinctly higher mortality rates. The mortality rate for labors that exceed thirty hours more than doubles, and for this reason it would seem reasonable to advocate consultation in all such cases unless the delivery is imminent.

TABLE VI. RELATIONSHIP OF FETAL AND NEONATAL MORTALITY TO METHOD OF DELIVERY

METHOD OF DELIVERY	TOTAL DELIVERED	TOTAL DEATHS	PERCENTAGE RATE
Spontaneous vertex	19,916	529	2.6
Low forceps	2,672	89	3.3
Midforceps	1,011	65	6.4
Cesarean section	782	57	7.3
Breech delivery	1,084	152	14.0
Version, extraction	182	42	23.1
High forceps	29	12	41.4
Craniotomy	38	38	100.0
Miscellaneous	-----	16	----

The methods by which the infants in this study were delivered is shown in Table VI. From the data, we note:

1. The lowest mortality rate (2.6 per cent) occurred in the spontaneous vertex deliveries. The low forceps group was slightly higher (3.3 per cent). This need not disconcert the advocates of the prophylactic low forceps since in both institutions the low forceps operation is done on definite indications only and for that reason our mortality rate in low forceps deliveries is not comparable with their figures.
2. A high gross fetal mortality rate in those patients delivered by cesarean section (7.3 per cent).
3. An extremely high mortality rate in the high forceps operation (41.4 per cent).
4. Almost one-fourth of the infants delivered by version extraction die. While this is an uncorrected figure, it appears unusually high and is explained largely by the fact that forceps are distinctly preferred to the version operation in both institutions. For this reason, version extraction is reserved for the more difficult cases in which forceps cannot be applied. Again this rate is

not comparable with the figures obtained by those who advocate wide indications for the version-extraction operation.

The gross infantile mortality in breech deliveries (14 per cent) warrants inquiry into the causes of death in these cases. This is shown in Table VII. Here we note that prematurity, congenital abnormalities,

TABLE VII. RELATIONSHIP OF BREECH DELIVERY TO CAUSES OF FETAL AND NEONATAL DEATH

CAUSES	NO. CASES (152)	DEATH RATE (PER CENT)
Prematurity	35	23.0
Asphyxia	28	18.4
Congenital abnormalities	26	17.1
Maceration	26	17.1
Birth injury	18	11.8
Congenital pneumonia and septicemia	9	5.9
Congenital syphilis	2	1.3
Erythroblastosis	2	1.3
Hemorrhagic disease	2	1.3
Liver abscesses	1	0.7
Aspiration of food	1	0.7
Diarrhea newborn	1	0.7
None	1	0.7
	152	100.0

and unexplained ante-partum deaths accounted for 47.2 per cent of the breech mortality. The causes of deaths that are more directly related to labor and to a large extent preventable, namely, asphyxia, birth injury, and pneumonia, accounted for 36.1 per cent of the breech deaths. In this latter group of causes asphyxia rather than birth injury ranked first.

A detailed study of the causes of fetal death in midforceps deliveries (Table VIII) showed that 46.1 per cent were due to birth injuries. The

TABLE VIII. RELATIONSHIP OF MIDFORCEPS DELIVERY TO CAUSES OF FETAL AND NEONATAL DEATH

CAUSES	NO. CASES (65)	DEATH RATE (PER CENT)
Birth injury	30	46.1
Congenital pneumonia	12	18.5
Asphyxia	9	13.9
Congenital abnormalities	4	6.2
Hemorrhagic disease newborn	3	4.6
Maceration	2	3.1
No cause	2	3.1
Prematurity	1	1.5
Erythroblastosis	1	1.5
Gangrene colon	1	1.5
	65	100.0

30 cases that make up this midforceps birth injury group would in themselves provide enough material for an interesting report. Categorically it may be stated that at least four types of errors were made in these cases, viz.:

1. Forceps were applied in the face of disproportion when a cesarean section should have been done.



2. Traction and rotation was not ideally adapted to the architecture of the pelvis.
3. Forceps were applied too late, after the fetus had been comprised by an excessively long labor which resulted in asphyxia or congenital pneumonia.
4. Traction was too rapid in an attempt to save the child from asphyxia.

As previously noted, the gross infantile mortality rate in cesarean sections was 7 per cent. This simply reflects the large number of cesarean sections that were done because of maternal complications irrespective of the fetal prognosis. A finding that caused some surprise was the fact that 5 of the 57 infants in this group died of a birth injury (Table IX).

TABLE IX. RELATIONSHIP OF CESAREAN SECTION AND THE INDICATIONS TO THE CAUSES OF FETAL DEATH

INDICATIONS	TERM	PRE-MATURE	TOTAL	FETAL DEATHS	
				CAUSE	NO.
Premature separation of placenta	10	14	24	Asphyxia	20
				Congenital abnormality	1
				Erythroblastosis	1
				Prematurity only	2
Placenta previa	4	6	10	Prematurity only	3
				Asphyxia	3
				Birth injury	1
				Congenital abnormality	1
				Congenital pneumonia	1
				No cause	1
Toxemia and/or chronic nephritis	0	6	6	Prematurity only	4
				Diarrhea, newborn	1
				Maceration	1
Cephalopelvic disproportion	5	0	5	Birth injury	2
				Congenital abnormality	1
				Erythroblastosis	1
				No cause	1
Cardiac	1	1	2	Birth injury	1
				Prematurity only	1
Constriction ring	1	0	1		
Fixed pelvic kidney	0	2	2	Congenital pneumonia	1
				Birth injury	1
				Prematurity	1
Acute yellow atrophy	1	0	1	Asphyxia	1
Posterior sacculation of uterus	0	1	1	Prematurity only	1

Ordinarily we are in the habit of associating birth injuries with the trauma of operative vs. pelvic deliveries or the trauma produced by a forceful rapid labor as the head is driven against a resistant pelvic floor, but apparently it would seem that the forces of labor may cause intracranial injuries under less obvious traumatic conditions. The actual

delivery of the child through the uteroabdominal incision was difficult in only one instance and this might have been the cause of the trauma in that case.

The discussion thus far has brought out the importance of asphyxia, birth injury, and congenital pneumonia as major causes of death in relation to the problems of labor. For this reason it would seem profitable to study these conditions in more detail, especially to determine how these deaths might have been prevented. Table X shows that these major causes of death are more distinctly problems that concern the term infant. The incidence of such deaths among the viable premature infants is decidedly less and in the very small previable premature infants their occurrence is negligible.

TABLE X. RELATIONSHIP OF MAJOR CAUSES OF FETAL AND NEONATAL DEATHS TO THE AGE OF THE FETUS

	PREVAILABLE PREMATURES (92)		VIALE PREMATURES (350)		TERM (558)	
	NO.	%	NO.	%	NO.	%
Birth injury	0	0	22	6.3	91	16.3
Asphyxia	4	4.3	44	12.6	150	26.8
Congenital pneumonia	0	0	7	2.0	62	9.3

The relationship of these major causes of fetal death to the time of death is shown in Fig. 2. The incidence of death due to asphyxia is highest during the ante-partum and intra-partum periods. Asphyxia, therefore, results largely in stillbirths, and it constitutes a distinct problem of labor. It is noteworthy that asphyxia is responsible for only a small number of neonatal deaths. It may well be that serious degrees of asphyxia usually prove fatal before the child is born, while the effects of lesser degrees of asphyxia are overcome once the child is born and respirations have been established. This is not entirely true, however, because there seems to be evidence to suppose that a child who has shown some evidence of intrauterine asphyxia and then is born alive may subsequently develop a pneumonitis from the effects of aspirated material. Such cases naturally would appear in the pneumonia rather than the asphyxia group.

Deaths due to pneumonia occur with greatest frequency during the intra-partum period, but if the child survives labor it is more likely to die at some time after the second hour of birth.

The deaths due to birth injury also occur most frequently during the intra-partum period, but they constitute the largest group that die during the first two hours post partum.

It is interesting to note that the general pattern of the curves noted in asphyxia, pneumonia, and birth injury, changes when the deaths due to prematurity are considered. Here we find that the ratio of stillbirths to neonatal deaths is reversed. Most premature babies die during the first twenty-four hours of life, a point which cannot be overemphasized in reference to their management.

In relationship to the duration of labor, all these major causes of death showed a decided increase in labors of thirty hours or more (Fig. 3).

When the method of delivery is studied in relation to the three major causes of infantile mortality (Table XI), it is noted first of all that the

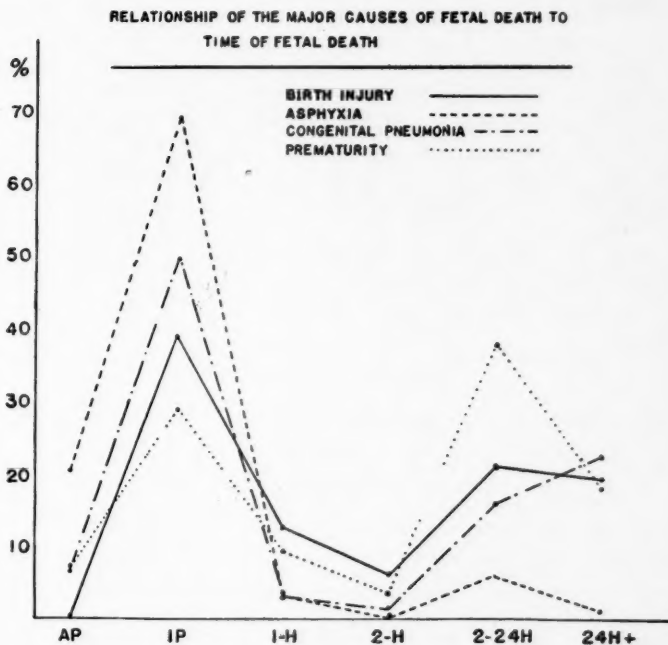


Fig. 2.

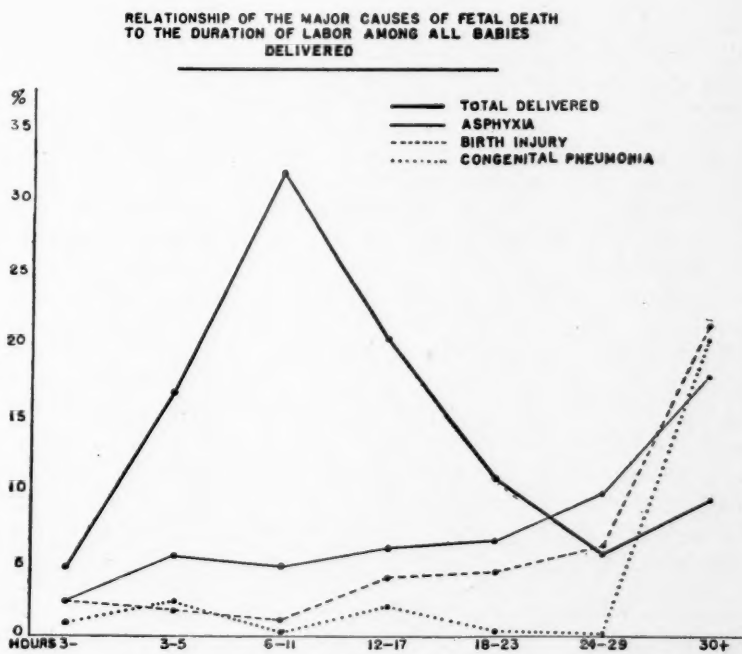


Fig. 3.

TABLE XI. RELATIONSHIP OF THE METHOD OF DELIVERY TO THE MAJOR CAUSES OF FETAL AND NEONATAL MORTALITY

METHOD OF DELIVERY	TOTAL DE-LIVERED	DEATHS FROM BIRTH INJURY		DEATHS FROM ASPHYXIA		DEATHS FROM CONGENITAL PNEUMONIA AND SEPTICEMIA	
		NO.	%	NO.	%	NO.	%
Spontaneous vertex	19,916	28	0.01	80	0.04	28	0.01
Low forceps	2,672	10	0.04	26	0.01	8	0.03
Midforceps	1,011	29	2.9	10	0.01	13	1.3
Breech delivery	1,084	18	1.7	27	2.5	8	0.07
Version, extraction	182	12	6.6	17	9.3	1	0.06
Craniotomy	38	7	18.4	3	7.9	11	28.95
Cesarean section	782	3	0.04	23	2.9	1	0.01
High forceps	29	6	20.7	3	10.4	0	0.0

birth injuries showed an increasing incidence as the more difficult operations are considered. The lowest incidence appeared in the spontaneous group (0.01 per cent) and the highest in the high forceps group (20.7 per cent). The risk of birth injury is greater in midforceps operations (2.9 per cent) than in breech deliveries (1.7 per cent).

In the cases of asphyxia, a somewhat similar relationship of increasing incidence with operative deliveries is noted. The very low asphyxia incidence in midforceps operations (0.01 per cent) is in contrast to the higher incidence of birth injuries in these operations (2.7 per cent), a point which should be borne in mind when forceps are used to deliver the infant that shows evidence of distress. The high incidence of deaths due to asphyxia among infants delivered by cesarean section (2.9 per cent) is explained by the relatively large number of cases of placenta previa and accidental hemorrhage in which the cesarean section was done primarily for maternal indications.

The deaths in the pneumonia group show no significant relationship to the method of delivery except for the very large number of these infants that were delivered by craniotomy (28.95 per cent). This is simply evidence of the large number of cases of pneumonia that died in utero.

Among all infants delivered at term, the incidence of large babies, which we arbitrarily chose to be 3,600 Gm. or over, was 33.1 per cent (Table XII). By comparison, the incidence of such term infants among

TABLE XII. RELATIONSHIP OF DEAD INFANTS WEIGHING MORE THAN 3,600 GM. TO THE MAJOR CAUSES OF FETAL AND NEONATAL DEATHS

CAUSES	NO. OF TERM DEAD INFANTS	NO. WEIGHING MORE THAN 3,600 GM.	RATE (PER CENT)
Birth injury	91	46	50.6
Asphyxia	147	56	38.1
Congenital pneumonia	62	23	37.1

Among all term babies delivered 33.1 per cent weighed 3,600 Gm. or more.

the deaths due to birth injury was 50.6 per cent. The large babies among the cases of asphyxia and congenital pneumonia also showed an increase above average but this was less striking than in the cases of birth injuries. Obviously the large size of the baby frequently is over-





the very end when it is reported that the fetal heart is very slow or has suddenly disappeared. When delivery is effected, the birth of the child is followed by a gush of blood and along with it appears the completely detached placenta. If the attendants are aware that such unfortunate cases of terminal placental separations occasionally occur and keep a constant watch over the fetal heart during the second stage, delivery may be carried out before the asphyxia becomes irreversible. To a large extent, therefore, the small number of deaths due to this type of premature separation of the placenta must be considered preventable.

The asphyxia deaths due to cord complications represent another large group which for the most part cannot be prevented. A study of these cases permits the following conclusions:

1. Cord complications should be suspected always when signs of fetal asphyxia develop in the absence of such maternal conditions as premature separation of the placenta, placenta previa, prolonged labor, and toxemia of pregnancy.
2. With the aim of detecting a prolapsed cord, the general rule is that the fetal heart must be auscultated after the membranes rupture. This would seem to be insufficient in many instances. The fetal heart may be perfectly normal immediately after the cord prolapses only to fail later on. The rule should be to the effect that the fetal heart must be carefully auscultated frequently during the half hour following the rupture of the membranes.
3. When the presenting part is unengaged and the membranes rupture, a cord prolapses often enough to make at least a rectal examination at that time of distinct value.
4. Tight loops of cord around the neck are hardly ever diagnosed until the child is delivered. It seems justifiable to suggest that when no other cause for the asphyxia is apparent, this condition should be suspected and the hand introduced to palpate the neck region. If this condition were known to exist before the actual delivery, the choice of operative procedures employed might be influenced by such knowledge.

The predisposing factors in asphyxia associated with prolonged labors are naturally related to the problems of dystocia in general. While the deaths due to birth injury in the presence of dystocia are not infrequently the result of unwarranted early interference, those due to asphyxia, on the other hand, are not infrequently the result of an overconservative policy of managing the labor. But while this overconservatism was displayed in the actual conduct of the labor, the delivery itself was often hastened because of a slowing fetal heart. If overconservatism in the management of labor proves to be an error, leading to a state of fetal asphyxia, then rapid delivery in the face of a failing heart simply multiplies the error.

While the factors which bring about asphyxia in placental and cord complications are obvious, those which are related to the asphyxia of the prolonged labor are not well understood. It is conceivable that prolonged labor results in intracranial vascular changes which in turn affect the fetal respiratory center, or what seems more likely, the more marked degree of uterine retraction with prolonged labor brings about

a state of relative ischemia of the entire uterine circulation resulting in interference with the efficiency of the uteroplacental exchange and subsequent fetal anoxia. In any event, the treatment of fetal asphyxia should begin by inhibiting uterine contractions with an anesthetic that permits a large admixture of oxygen such as ether. The fetal heart is watched constantly and as long as the rate shows gradual acceleration, even if the degree of such acceleration is slight, no attempt whatsoever is made to deliver the child. Nearly always after a period of five to ten minutes the fetal heart becomes restored to a normal rate. At this stage the mother should be receiving oxygen in maximal amount and just sufficient anesthesia to prevent uterine contractions. Under these conditions delivery may be carried out slowly and deliberately. This method of treating the asphyxiated child falls in line with the present-day surgical principle of treating the patient, which in this case is the unborn child, so that he is in the best possible condition before any surgical procedure is attempted.

Asphyxia was of unknown origin in fourteen term infants. There was nothing about their deaths which we could relate in any way to the mechanism of asphyxia either clinically or pathologically.

Asphyxia was due to toxemia of pregnancy in 6 cases. While the infantile mortality rate is high in severe toxemia, the cause of these deaths is not definitely understood, because the fetus is so frequently macerated that very little pathologic study is possible. While most of the deaths due to toxemia in this series, therefore, are entered in the large group of macerated babies or among the asphyxias due to premature separation of the placenta, a small group showed pathologic evidence of asphyxia without demonstrable cause other than the toxemia. It is assumed that the toxemic state so alters the uteroplacental exchange that the fetal circulation becomes severely compromised.

As we had planned this survey originally, a study of the influence of analgesics on asphyxia and fetal deaths in general was contemplated, but the time intervals of administration of drugs were not recorded with sufficient accuracy to give value to such an analysis. Only isolated instances could be satisfactorily evaluated. There were four cases in which analgesic drugs were given in large enough dosage to be considered unequivocal factors in the asphyxia.

TABLE XIV. PREDISPOSING FACTORS IN ALL CASES OF BIRTH INJURY

FACTORS	TERM	PREMATURE
Cephalopelvic disproportion	22	0
Uterine inertia (some due to narcosis)	16	0
Not known	11	7
Malposition		
Breech	9	5
Brow	4	0
Face	1	0
Forceps trauma and/or bad mechanics	8	1
Rapid, hard labor (some without analgesia)	6	3
Rapid expulsive labor following medical induction	3	2
Trauma from version, extraction (no other cause)	1	3
Asphyxia with rapid delivery	3	0
Prolonged second stage	3	0
Obstruction from myomas	2	0
Constriction ring	2	0
Forceps trauma in cesarean section	0	1

In the remainder of the asphyxia group, the cases that merit comment are those in which pituitary extract proved disastrous. Although an indispensable drug, its use before delivery at times becomes hazardous. There were apparently more bad effects when the pituitary extract was administered intranasally. It would seem that when given in this way the dosage is indeterminate and that in some cases more of the drug may be absorbed than can be tolerated with safety. The intramuscular administration starting with doses as low as one minim to ascertain the patient's sensitivity to the drug would seem to be a much safer procedure.

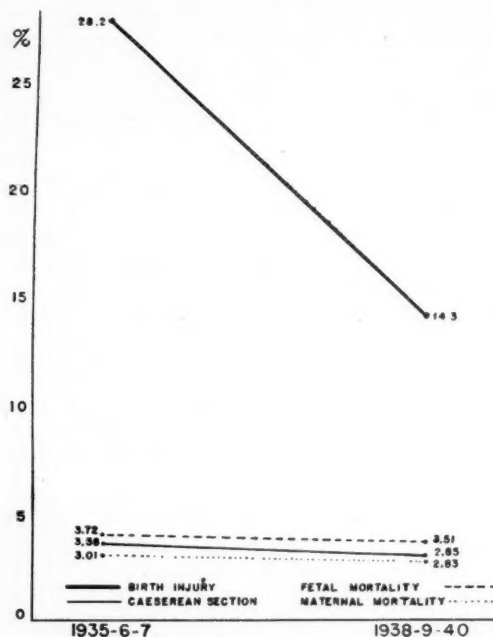


Fig. 4.

As might well be expected, the most important predisposing factor in the cases of birth injury was cephalopelvic disproportion (Table XIV). If the limitations of the pelvis had been accurately known in the 22 cases which fall in this category, a well-timed cesarean section would have saved most of these babies. As these birth injuries were being reviewed, it occurred to us that there were many more such cases among the older records than among the more recent ones. On analysis this proved to be true (Fig. 4). There was a reduction in the incidence of birth injuries from 28 per cent of all fetal deaths in 1935, 1936, and 1937 to 14 per cent of all fetal deaths in the years 1938, 1939, and 1940. This occurred without any rise in the cesarean section or fetal mortality rate. On the contrary, both the cesarean section rate and the fetal mortality rate showed a slight fall in the more recent years. In explaining these results, we believe that adequate emphasis should be placed upon the aid that x-ray pelvimetry has given us. In our combined experiences, this has been the most important contributory factor in the reduction of the incidence of birth injuries. Roentgenologic pelvimetric studies have



not only aided us in choosing the cases of cephalopelvic disproportion early in labor when the cesarean section operation can be done with comparative safety, but they have enabled us to use better mechanics in operative pelvic deliveries.

The cases of birth injury associated with uterine inertia present a real problem, for in this group all the refinements of prognostic acumen may fail. There is no certain method of determining whether a patient with primary uterine inertia will develop efficient uterine contractions as labor advances or continue to have desultory ineffectual pains throughout the entire labor. There is real need for an accurate method by which a qualitative interpretation of the uterine contraction may be made.

In eighteen cases the predisposing cause of the birth injury was not apparent from the records. While this might be expected in a certain number of the premature babies, it is difficult to explain the 11 cases that occurred in term infants. We can only conclude that such factors as cephalopelvic disproportion, forceps trauma, and bad mechanics frequently go unrecognized, although it should be restated here that the forces of labor in the course of molding and descent occasionally may cause damage to the fetal head even when there is no apparent trauma. This was shown in the analysis of the cesarean section group.

Just as there should be condemnation of the excessive use of analgesia leading to a state of uterine inertia, so we condemn the failure to use these valuable drugs when the patient develops unduly forceful frequent contractions that characterize precipitous labors. Rapid labor whether it develops spontaneously or is the result of induction should be treated with proper sedatives or anesthesia to avoid intracranial injury.

A small but sad group of cases are the three babies that sustained intracranial injuries when attempts were made to save them from asphyxia. Again, in these cases, better management of the asphyxiated baby might have given different results.

The factors which predispose to congenital pneumonia (Table XV) seem to fall into a fairly definite pattern. We have first those factors

TABLE XV. PREDISPOSING FACTORS IN ALL CASES OF CONGENITAL PNEUMONIA AND SEPTICEMIA

FACTORS	TERM	PREMATURE
Premature rupture of membranes, uterine inertia, prolonged labor, intra-partum infection	28	1
Premature rupture of membranes with normal labor	13	1
Not known	7	5
Inadequate pelvis and prolonged labor	6	0
Prolonged labor and:		
Narcosis	2	0
Large baby, breech	1	0
Constriction ring	1	0
Medical induction	1	0
Premature rupture membranes and maternal pneumococcus infection	1	0
Congenital anomaly of the heart	1	0
Erythroblastosis	1	0

that predispose to a prolonged labor, namely, uterine inertia and cephalopelvic disproportion, and to them has been added the premature rupture

of the membranes. The problem, therefore, is not fundamentally different from that noted in birth injury and asphyxia, for it could be said that if the membranes had not ruptured many of these babies would have survived up to the time of delivery, only to be subjected to the same hazards encountered in those groups. They belong in the pneumonia group, therefore, rather than in the birth injury or asphyxia group because the accidental early rupture of the membranes exposed them to an infection which caused their death before they could be exposed to trauma or asphyxia.

While this form of reasoning may apply to many of the pneumonia cases, it does not apply to all, for we note that in 14 cases labor was normal and there is every reason to believe that, had the membranes remained intact, a living child would have resulted. There is an important lesson to be learned from these 14 cases in connection with the artificial rupture of the membranes either to induce or hasten labor. While premature rupture of the membranes is not usually attended with serious consequences, the possibility of a fetal pneumonia should not be completely dismissed from the mind. A good rule to follow should be to the effect that the membranes should be preserved at all times unless there is reason to believe that the termination of labor will not be long delayed after their rupture.

In Table XVI it is noted that 27.4 per cent of all premature labors occur without cause. Premature rupture of the membranes could not be listed as a separate predisposing cause of premature labor, because one does not know whether the rupture of the membranes occurs as an accidental predisposing incident unrelated to labor itself or as a concomitant part of the premature labor. It was somewhat surprising

TABLE XVI. PREDISPOSING CAUSES OF PREMATURE LABOR

CAUSE	NO. CASES	PERCENTAGE
No cause (including premature rupture membranes)	116	27.4
Dead fetus	113	26.7
Congenital abnormalities	51	12.0
Premature separation of placenta	24	5.7
Multiple pregnancy	22	5.2
Therapeutic interference	17	4.0
Placenta previa	17	4.0
Toxemia	13	3.1
Hydramnios (no congenital abnormalities)	7	1.7
Acute pyelitis	7	1.7
Multiple myomas	6	1.4
High amputation of cervix	5	1.2
Footling breech	4	0.9
Undelivered	4	0.9
Maternal pneumonia, influenza	4	0.9
Cesarean section	3	0.7
Bicornuate uterus	2	0.5
Severe anemia	1	0.2
Tuberculosis with high fever	1	0.2
Ruptured cesarean scar	1	0.2
Following radical mastectomy	1	0.2
Following fall	1	0.2
Injection varicose veins with quinine	1	0.2
Cachexia, gastric cancer	1	0.2
Self-induced	1	0.2
	423	99.6

to find so many cases in which there were definite predisposing factors of premature labor. An analysis of these factors brings out a large number of unrelated conditions which throws very little light on the problem of preventability except for (1) 5 patients in whom there had been a high amputation of the cervix, (2) 3 patients in whom a cesarean section was done too early in the period of gestation, and (3) 1 patient who received injections of quinine for the treatment of varicose veins.

#### DISCUSSION

With the realization that the presentation of our study includes many facts which conform to statistics previously reported and substantiates in percentages what some have already known to be true from many years of experience and teaching, we should like to emphasize that our results and observations, entirely based on a critical analysis of all the cases included in the scope of our study, represent the combined experience of the Sloane Hospital for Women and the Lying-in of the New York Hospital. Each history was carefully reviewed, and we feel that the expenditure of time that was demanded fully repaid our efforts, since in most cases we were able to arrive at a satisfactory evaluation of the data recorded.

The results, as they have been reviewed, immediately become associated with the subject of preventability. How might we have arrived at a lower fetal and neonatal mortality rate during the period considered in our analysis? How may we benefit now from our experiences in the immediate past? How will we be able to reduce fetal and neonatal mortality in the future? It would be presumptuous to assume that these questions can be fully and satisfactorily answered. However, in the light of our analysis, the following comments seem worthy of consideration.

A note of conservatism dominates the practice and teaching of obstetrics in the two clinics represented in the study. Although we cherish that note, fair criticism can be directed to a representative number of cases in which earlier interference might have saved the baby. Cases of prolonged labor without appreciable progress leading to fetal distress with subsequent asphyxia and instances in which the presenting part was allowed to remain on the pelvic floor and in midpelvis too long during the second stage are examples.

It appears that a more judicious use of oxygen and ether anesthesia in cases where the fetus begins to show early signs of distress in utero might have prevented fatal asphyxia. Too frequently operative interference by the application of forceps, breech extraction, or version and extraction was untimely hurried in instances of fetal distress, especially when following vaginal examination the cervix was found "almost" completely dilated. More oxygen and ether anesthesia and less hurry might have prevented fetal death under such circumstances.

Asphyxia resulting from terminal separation of the placenta might not have proved fatal with more active vigilance during the second stage.

There were a considerable number of cases in which the cord prolapsed following rupture of the membranes. Since most of these were associated with abnormal presentations and floating heads and because the accident, in many cases, was not detected until a comparatively long interval after its occurrence, it seems that a number of babies might not have died of asphyxia had the obstetrician known of the prolapse promptly and acted accordingly. Patients in active labor with abnormal presentations and floating presenting parts should be carefully followed and examined for a prolapsed cord soon after the membranes rupture.

Too much care and discrimination in the use of oxytocics during labor cannot be exercised. Primary fetal asphyxia and asphyxia secondary to premature separation of the placenta, while only a few in number, resulted from the administration of pituitrin.

A consideration of birth injuries reveals that disproportion and bad mechanics in the application of and extraction with forceps accounts for a greater part of the unhappy outcomes. Unquestionably, a timely cesarean section was indicated and would have saved the baby in many instances. To cope with this problem, it becomes evident that we should be incessantly striving for a more accurate evaluation of each individual case. Today we believe that x-ray pelvimetry is one of the invaluable adjuncts which is enabling us to refine our judgment and decision in making better selection of these cases for cesarean section and forceps delivery.

Medical induction with quinine and with or without pituitrin is not an obstetric procedure without potential hazard. Rapid and expulsive labors following medical induction with subsequent birth injury or asphyxia to the fetus are not rarities. For this reason, only the most justifiable indications should be current whenever a medical induction is contemplated.

The different individual factors and combination of factors influencing fetal mortality are much too great to enumerate and consider. However, prevention of fetal deaths as well as maternal deaths is still intimately related to better ante-partum care, better obstetric training, improvement in operative procedures and techniques, and so far as the neonatal baby is concerned, a better understanding of its immediate pediatric problems.

Primary uterine inertia, premature labor, premature rupture of the membranes, the effect of analgesia on fetal respiration and circulation, the onset and mechanism of labor, are major problems which remain beyond our complete understanding. The hope of the future lies in their solution. True, great strides have been made. For example, researches on x-ray pelvimetry are beginning to give us some insight on the effect

of the forces and mechanism of labor, endocrinology is advancing our knowledge of the physiology of the uterus, and the work of Snyder and many others is contributing newer concepts of intrauterine respiratory physiology and the effect of drugs and anesthetics on fetal respiratory and circulatory centers.

In striving to reduce fetal mortality, we cannot lose sight of its reciprocal, maternal mortality. The two are inseparable so far as they reflect the brand of our obstetric practice, since one cannot be fundamentally sacrificed at the expense of the other. The best obstetrics will always be projected in our constant efforts to reduce both infantile and maternal mortality.

#### SUMMARY

1. The study is concerned with a report of 1,000 fetal deaths occurring among 25,823 deliveries at New York Hospital and the Sloane Hospital for Women. On the basis of live births, the gross fetal mortality rate was 4.03 per cent. If only the viable infants are included, the rate is 3.66 per cent.

2. Asphyxia is the most common cause of fetal death.

3. There is a higher fetal death rate in the Negro.

4. Multiparas and primiparas show essentially the same fetal death rate.

5. The greatest net gain of living over dead children occurs among women between 20 and 24 years of age. After the age of 30 the woman delivers a proportionately greater number of dead babies than she did before that age.

6. In labors that exceed thirty hours, the fetal mortality rate doubles.

7. Spontaneous deliveries show the lowest fetal death rate. High forceps show the highest.

8. On the basis of the material studied, a reduction of the fetal death rate suggests the following:

- (a) Labors that exceed thirty hours in duration should receive the benefit of consultation, unless delivery is imminent.

- (b) Interference should be avoided unless absolutely justifiable; the best results are obtained in spontaneous deliveries.

- (c) Pelvic conformation should be studied roentgenologically if there is doubt. Both see and feel the cephalopelvic relationship.

- (d) The mechanism of delivery should be adapted to the architecture of the pelvis in operative deliveries.

- (e) In dystocia, avoid interference if progress is being made even though the progress is slow, but do not unnecessarily delay delivery if progress has come to a standstill.

- (f) The asphyxiated baby should be treated before delivery. Avoid hurry in delivering these babies.

- (g) The fetal heart should be auscultated frequently for one-half hour after membranes rupture.



(h) Examine patient after the membranes rupture if the presenting part was high prior to their rupture.

(i) Examine for tight cord around neck when there is no other obvious cause for asphyxia.

(j) Use sedatives sparingly when labor is going to be prolonged. Use them freely in cases of precipitate labors.

(k) Use pituitrin with great care if at all before parturition.

(l) Save premature babies by adequate pediatric organization. The first twenty-four hours are the most important.

(m) Research in the causes of labor, the causes and early detection of uterine inertia, the causes of premature rupture of membranes, means of predetermining the size of the fetus, the physiology of fetal respiration, the mechanics of molding and birth injuries, and the physiology of the premature infant will all aid materially in further reducing the infantile mortality rate.

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### THE CLINICAL SIMILARITY OF CORPUS LUTEUM CYST AND ECTOPIC PREGNANCY

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THERE is, perhaps, no better known and no more dramatic condition in gynecology than that of ruptured tubal pregnancy with massive intraperitoneal hemorrhage. The classical picture of sudden, severe, tearing pain in the lower abdomen followed by shock in a woman of childbearing age offers little chance for diagnostic error. It is, moreover, not essential that the diagnosis in such instances be precise, for laparotomy is obviously and urgently required. A diagnostic problem is encountered, however, in either the unruptured variety of tubal pregnancy or the type which causes a slow intra-abdominal hemorrhage through the tubal lumen, tubal abortion. Many of the patients coming within either of these two groups of tubal gestation, the unruptured and the tubal abortion, present symptoms so mild, complaints so bizarre, and physical signs so vague that it is not unusual for the illness to be misinterpreted. When the patient's history fits into the textbook pattern of ectopic gestation, irregular uterine bleeding following a missed period and accompanied by recurrent episodes of lancinating pain in the lower abdomen, its recognition offers little difficulty. This conventional clinical picture of either unruptured tubal pregnancy or tubal abortion is, however, occasionally mimicked to a most surprising degree by another, less serious, intrapelvic disorder, the corpus luteum cyst.

Rokitansky described the corpus luteum cyst as a pathologic entity in 1859. Years later, when ovarian changes were first being correlated with aberrations of the menstrual cycle, several gynecologists (R. Meyer, Ruge II, Pischzek, and others) observed the association of delayed menstruation with the persisting, usually cystic, corpus luteum. The clinical similarity of tubal abortion and corpus luteum cyst was first recognized by Halban<sup>1</sup> in 1915. In reporting his several experiences in mistaking a simple lutein cyst for tubal gestation, Halban stated: "The usual story is that a woman reports with the complaint of early amenorrhea, believing herself pregnant. The examination reveals a slightly enlarged uterus and, more important, a soft tumor in either the right or the left adnexa. If the physician knows the patient and recalls that no such tumor was present at previous examinations, he must entertain the suspicion that he is dealing with an extrauterine pregnancy. Such a suspicion led me in several instances to perform a laparotomy with the expectation of removing a pregnant tube. In place of this, however, a cystic tumor of the ovary and no trace of ectopic pregnancy was found."

Every gynecologist sooner or later experiences similar chagrin and surprise after performing a laparotomy on a patient with a seemingly typical example of tubal abortion only to be quite taken aback in discovering a small and relatively insignificant corpus luteum cyst. While this simulation is widely recognized, it is not generally appreciated that the laboratory findings in these two conditions may be alike.

This presentation was undertaken not only to re-emphasize the remarkable resemblance which the syndrome created by an abnormally persistent corpus luteum may bear to extrauterine pregnancy, but also to draw attention to the fact that the degree of mimicry may be heightened, as illustrated in the histories abstracted herein, by the presence of a positive Friedman test and the finding of well-developed deciduallike changes in the endometrium.

#### PATHOGENESIS OF THE CORPUS LUTEUM CYST

The etiology of the simple retention cyst of the corpus luteum is not clear. "It is possible," states Novak,<sup>2</sup> "that at times the cystic distention of a corpus luteum for some unknown reason is so great as to interfere with the normal involution of the lutein layer, thus resulting in the so-called *corpus luteum persistens*." Inasmuch as the corpus luteum cyst is usually found in an otherwise perfectly normal ovary of a woman free from any recognizable ailment, the mechanism of its formation is usually rather loosely ascribed to "perverted physiologic activity."

Shortly after Halban's description of the clinical syndrome, Wagner,<sup>3</sup> in reporting two instances of a falsely positive Aschheim-Zondek pregnancy test in association with a corpus luteum cyst, postulated the origin of the cyst to be hyperpituitary function. One of Wagner's patients exhibited the signs and the symptoms of a benign pituitary adenoma which seemingly yielded to roentgen ray treatment. Others, who obtained a positive biologic pregnancy test in the presence of surgically proved instances of corpus luteum cyst, also assumed that the

presence of an excessive quantity of hypophyseal gonadotropin is responsible for both the persistent corpus luteum and the positive pregnancy test.<sup>4</sup>

Although it is a most attractive and simple theory, it cannot yet be unequivocally stated that the corpus luteum cyst is the result of disordered pituitary function. It can be stated, on the basis of the clinical data and the pathologic findings, that such a cyst represents an abnormal retrogression of the lutein stage and that its association with an excessive excretion of gonadotropin suggests the existence of a temporary state of hyperpituitarism.

Pathologically, a corpus luteum cyst must be differentiated from the follicle cyst and the atretic follicle cyst, and from the mature corpus luteum. All of these structures may be similar macroscopically, attaining the maximum size of a walnut and possessing a small central cavity filled with either coagulable serum or blood. The yellow color often exhibited by the smooth, glistening interior of such a walnut-sized cyst is not necessarily pathognomonic of corpus luteum tissue. The yellow hue may, of course, represent lutein cells, but it may also be derived from lipid deposits, blood pigment within phagocytes, or luteinized cells of the theca interna.<sup>5</sup> Microscopic study of the wall of such yellow cysts enables one to distinguish the basic morphology. The follicle cyst is identified by the characteristic granulosa cells and the small, crowded cells of the surrounding theca interna. The atretic follicle cyst is recognized by the flattened granulosa layer and the well-preserved, often luteinized, cells of the theca interna. The mature corpus luteum is characterized by its layer of large, polyhedral lutein cells, the outer border of which is penetrated at intervals by v-shaped, capillary-laden bands of luteinized theca cells.

The corpus luteum cyst, representing merely the persistent shadow of a formerly mature corpus luteum, exhibits the substance of the latter in altered form. The histologic appearance of the cyst depends on its age. In the beginning, the lutein layer may be fairly well preserved (Fig. 2). As the blood supply diminishes, fatty degeneration and fibrosis so change the architecture of the layer that it is often unrecognizable. Moreover, its formerly large cells become pyknotic as a result of compression by the semisolid coagulum of the cystic cavity. As time goes on, connective tissue is deposited between the lutein tissue and the centrally contained material, a process which finally results in a densely fibrinous inner lining (Fig. 1).

#### DIFFERENTIAL DIAGNOSIS OF CORPUS LUTEUM CYST AND TUBAL ABORTION

It would be well were one able to differentiate an ectopic gestation from a corpus luteum cyst preoperatively, because the latter does not usually require surgical intervention. The clinical attempt to distin-



guish the two conditions must take into consideration the likeness in symptomatology, the similarity of the pelvic signs, and a possible parallelism of certain laboratory findings. The latter may include an excessive excretion of gonadotropin, the histologic characteristics of the endometrium, and the urinary level of pregnanediol. The brief discussion and the several case histories presented in the following paragraphs do not clarify the problem of establishing a correct preoperative diagnosis. They serve rather to reassert the frequent impossibility of so doing and to surround such errors in diagnosis with an aura of plausibility.

*Symptomatology.*—The symptoms evoked by the persisting corpus luteum and its eventual successor, the corpus luteum cyst, vary with the passing of time. The clinical pattern parallels the gradual change from an active gland of internal secretion producing estrogen and progesterin to a functionless, vestigial-like cyst. There is at first a brief period of amenorrhea which is followed, as the luteal tissue distinegrates, by an episode of irregular uterine bleeding. It is this reversal of menstrual function, together with the tender adnexal mass it creates, which causes the corpus luteum cyst to be confused with extrauterine pregnancy. The clinical parallelism may be magnified by the presence of certain of the presumptive signs of pregnancy in women with a persistent corpus luteum. Van Tongeren<sup>6</sup> and others, commenting on the semblance of this condition to pseudopregnancy in animals, reported concerning the presence of vaginal lividity and cervical softening in such patients. The occurrence of these changes, evidence of a superabundance of the ovarian hormones, is readily understood when it is recalled that functioning lutein cells secrete *both* estrogen and progesterin. The following case history illustrates the deceptive symptoms and the misleading local signs of pregnancy sometimes evoked by the corpus luteum cyst:

CASE 1.—(Mount Sinai Hospital, No. 95874.) M. V., a secundipara, aged twenty-five years, regular menstrual cycle every thirty days, had had her last menstrual period on July 20, 1935. The August and September periods had been missed, and the patient thereafter experienced brief, recurrent episodes of lancinating pain in the left lower portion of the abdomen. On September 27, believing herself pregnant, the patient attempted to induce an abortion by introducing a rubber catheter into the cervical canal. Several days later, slight bleeding ensued and persisted intermittently for a month, in association with repeated attacks of the left-sided pain and without the passage of either clots or tissue. On November 6, a Friedman pregnancy test was negative. At the time of her hospitalization on November 8, examination showed cyanosis of the vagina, softening of the closed cervix, suspected uterine enlargement, and a plum-sized mass of the left adnexa. The latter seemed unusually tender. The following day, a small quantity of grossly nondescript endometrial tissue was recovered from the uterine cavity by curettage, and exploration of the abdomen revealed a thick-walled, corpus luteum cyst of the left ovary which was removed. Histologically, the endometrium was hyperplastic but showed several areas of secretory change, and the corpus luteum cyst possessed a densely fibrinous lining, a finding which affirmed the apparent chronicity of the cyst (Fig. 1).

*Pelvic Examination.*—The local characteristics of the corpus luteum cyst are not sufficiently distinguished by bimanual pelvic examination to enable a clear differentiation from early tubal pregnancy. The cyst is usually palpable as a walnut-sized, smooth, somewhat mobile, adnexal tumor. Its consistency varies with the content of its central cavity, being either soft or tense. Unless it is ruptured, an event occasionally caused by the bimanual examination, and associated with intra-peritoneal bleeding, the corpus luteum cyst is ordinarily much less tender to palpation than the average tubal gestation. This alone, however, is not a sufficient criterion upon which to base a differential diagnosis. The following case report emphasizes the possible error which might occur when there is a too eager interpretation of a tender adnexal mass as a tubal pregnancy:

CASE 2.—(Mount Sinai Hospital, No. 10896.) N. L., a tertipara, aged 23 years, was admitted to the hospital on July 20, 1937, because of repeated attacks of sharp pain in the right lower abdomen during the

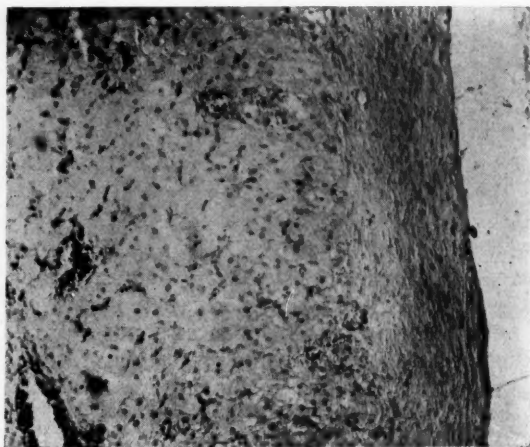


Fig. 1.—Photomicrograph of corpus luteum cyst (Case 1), showing a dense layer of fibrin between the central cavity and the lutein cells.  $\times 135$ .

preceding five days. Her menstrual cycle was of the twenty-five-day type, and the last period on June 30 had been scanty. Vaginal spotting was noted on July 18, three days after the onset of abdominal pain. Examination showed a soft, tender, right adnexal tumor the size and shape of a hen's egg. Abdominal exploration, on the provisional diagnosis of unruptured tubal pregnancy, revealed the palpable mass to be a corpus luteum cyst containing a soft blood clot. On histologic study, the lutein cells were clearly recognizable (Fig. 2).

*Excretion of Gonadotropin.*—The biologic pregnancy test, depending upon the excretion of chorionic gonadotropin in the urine of the pregnant woman, is of no value in differentiating intrauterine from ectopic pregnancy. It is generally conceded, however, that the test when positive is important in distinguishing tubal pregnancy from all other recent adnexal masses. Since a positive Aschheim-Zondek or Friedman test in pregnancy indicates living chorionic tissue, a negative reaction

merely implies the converse, the absence of living chorionic tissue. It is possible, therefore, to obtain a negative biologic test in instances of tubal gestation wherein the conceptus has ceased to grow. Experience has proved that a negative Friedman test does not exclude the possibility of ectopic pregnancy and is, thus, meaningless in the differential diagnosis of a tender adnexal tumor. When such a mass is under alert scrutiny, the value of a thoroughly trustworthy positive pregnancy test becomes apparent. The observations of other gynecologists<sup>3, 4</sup> concerning the falsely positive pregnancy test associated with the persistent corpus luteum cast a shadow of doubt upon the reliability of the positive reaction under circumstances leading to the suspicion of ectopic pregnancy. The two case histories which follow serve as practical illustrations of this problem:

CASE 3.—(Hospital of the University of Pennsylvania, Gyn. Nos. 24761 and 24784.) H. F. W., a secundipara, aged 24 years, who



Fig. 2.—Photomicrograph of corpus luteum cyst (Case 2) in which the theca interna, layer of lutein cells and the loose central coagulum are clearly recognizable.  $\times 95$ .

normally had menstrual cycles with a twenty-eight-day interval and a seven-day flow, had had her last menstrual period on Jan. 8, 1935. On February 13, when her expected period was a week overdue, vaginal spotting and intermittent, colicky pain in the lower abdomen occurred. A Friedman test for pregnancy was positive at that time. On February 25, she was admitted to the hospital because of persistence of both the slight metrorrhagia and the pain. Pelvic examination disclosed no abnormalities other than a retroflexed uterus which was easily placed into an anterior position and maintained therein by a Hodge vaginal pessary. The patient was discharged in twenty-four hours, the diagnosis being "early threatened abortion complicated by uterine malposition." She was readmitted ten days later, on March 8, because of increased uterine bleeding and localization of the recurrent pain in the right lower portion of the abdomen. Bimanual examination under anesthesia, following the removal of the pessary, revealed a tense, walnut-sized mass to the right of a retroflexed uterus of normal size. Diagnostic curettage

disclosed no signs of trophoblastic tissue (Fig. 3). Laparotomy showed the adnexal tumor to be a hemorrhagic corpus luteum cyst (Fig. 4).

CASE 4.—(Hospital of the University of Pennsylvania, Gyn. No. 25377.) A. M., a tertipara, aged twenty-eight years, whose menstrual cycle usually had thirty days of interval and three days of flow, was admitted to the hospital on Sept. 19, 1935, because of suspected ectopic gestation. Her last period, on July 6, had been but a "15-minute flow."

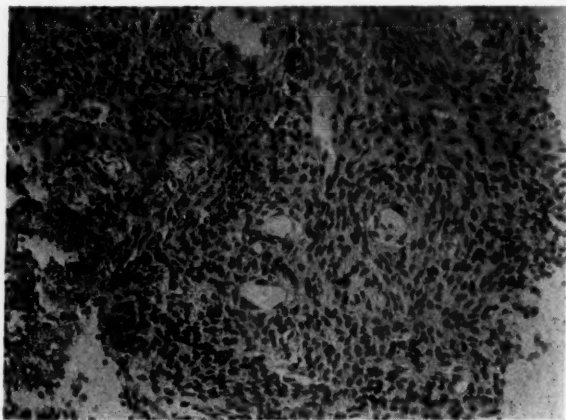


Fig. 3.—Photomicrograph of specimen of endometrium (Case 3) recovered by curettage, showing no chorionic villi. Note the decidualike stromal cells.  $\times 250$ .

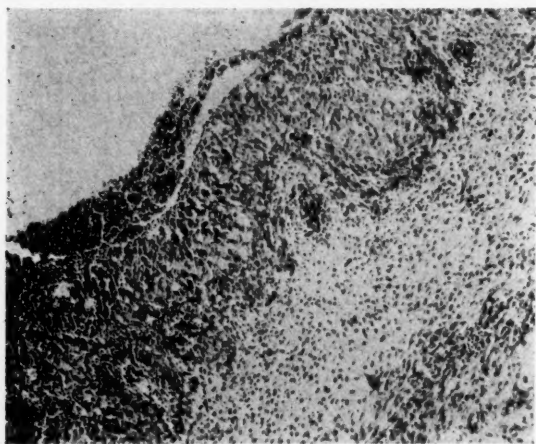


Fig. 4.—Photomicrograph of hemorrhagic corpus luteum cyst (Case 3). Note the blood clot adherent to the layer of lutein cells.  $\times 135$ .

Morning nausea and vomiting, mastalgia, and stabbing pain of the lower abdomen occurred early in September. Friedman test was positive on September 15. Examination revealed a normal uterus and exquisitely tender right adnexa. No mass was delineated. Diagnostic curettage recovered a scanty quantity of endometrial tissue. Abdominal exploration disclosed, in addition to tuberculosis of the ileum, a follicle cyst of the right ovary containing a fresh blood clot and showing on histologic study, luteinization of the granulosa cells (Fig. 5).



The two histories abstracted above emphasize the well-known fact that a positive Friedman reaction also occurs in a wide variety of conditions other than pregnancy, conditions which are associated with an *excessive* excretion of gonadotropin. In the absence of chorionic tissue, the Friedman test may, therefore, be considered a fairly good qualitative measure of overactivity of the anterior lobe of the pituitary gland. When faced with the necessity of interpreting such a positive Friedman test, the physician must consider several clinical possibilities. This dilemma is well stated by McCullagh and Cuyler,<sup>7</sup> as follows: "Theoretically, an excess of pituitary gonadotropic hormone might be expected in cases of tumor, and irritative lesions of the pituitary. It should occur in cases of pituitary hyperactivity caused by excessive stimulation from the nervous controlling mechanism, or in the presence of hyperactivity resulting from deficiency of the normal inhibiting factors such as might result from damage to the ovaries or testes." Accordingly, the positive

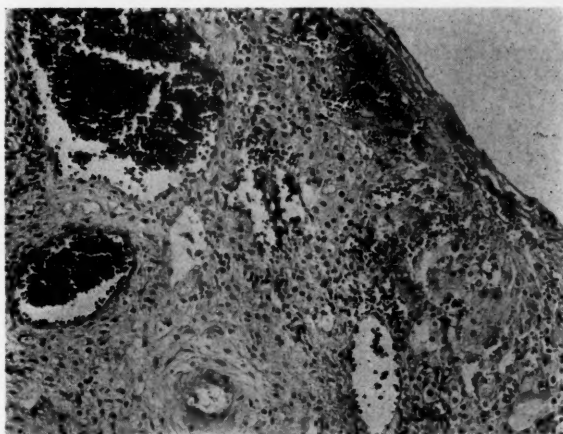


Fig. 5.—Photomicrograph of corpus luteum cyst (Case 4), showing intense hyperemia and well-preserved lutein cells.  $\times 135$ .

Friedman reaction in nonpregnant women with a corpus luteum cyst may be the result either of an unknown disorder affecting the little understood nervous center of the anterior hypophysis or of a diminished production of progestin and estrogen by the lutein cells. Nothing can be said at the present time concerning the former possibility. However, the latter, subnormal endocrine function of the granulosa cells at the very onset of luteinization, affords a logical, theoretical explanation for the presence of excessive pituitary gonadotropin in the urine. The anterior hypophysis, uninhibited by the low level of ovarian hormones, secretes additional gonadotropic substance in order to support the apparent failure of luteinization and responds too generously. The inordinate quantity of pituitary gonadotropin so produced may result in both the positive Friedman reaction and the oversupported, nonregressive, persistent corpus luteum. This credible hypothesis, as previously noted, is not readily proved.

*Endometrial Pattern.*—The development of decidual changes in the endometrium in association with ectopic pregnancy is universally con-

ceded. However, the number of patients in whom it is found is equivocal, varying inversely with the prior duration of the uterine bleeding.<sup>8</sup> The probability of recovering decidua from the curettings naturally lessens as the time of the bleeding lengthens because the decidual tissue is shed constantly as small fragments. Uterine curettage is, therefore, of some diagnostic value in obscure instances of suspected ectopic pregnancy only if the period of uterine hemorrhage is short. While the presence of decidua without chorionic villi may be considered presumptive evidence of extrauterine pregnancy, its absence under such circumstances does not necessarily exclude the possibility. The interpretation of the curettings obtained for diagnostic purposes in a patient presenting the history of an extrauterine pregnancy is made more difficult by the fact that excessive and prolonged action of the corpus luteum may create a decidualike pattern in the endometrium (Figs. 3 and 6). The degree of pseudodecidual response in the endometrium depends, quite naturally, on the quantity of progesterin secreted by the corpus luteum. Since this function of the lutein cells apparently varies widely, as gauged by the fluctuations in the amount of progesterin excreted in the urine as pregnanediol during the luteal phase of the menstrual cycle in normal women,<sup>9</sup> it is readily understood that all gradations of pseudodecidua may be encountered. Te Linde and Henriksen<sup>10</sup> recently drew attention "to the possibility of a decidualike response of the endometrium to progesterone in the absence of pregnancy." The latter authors described several patients with decidual reaction of the endometrium in whom the presence of pregnancy seemed to be either well excluded or quite improbable. The photomicrographic evidence presented and the literature cited by Te Linde and Henriksen substantiate the belief that it is possible for decidua to form in the absence of a fertilized ovum. The endometrium of one of the patients in this series, whose case history follows, presented an excellent example of such pseudodecidua:

CASE 5.—(Mount Sinai Hospital, No. A 14204.) J. R., a secundipara, aged thirty-six years, who usually had a twenty-eight-day menstrual cycle, was admitted to the hospital on Aug. 1, 1939, because of the suspicion of tubal abortion. Her last period had been skipped. Vaginal spotting occurred initially early in July. Cramplike pains, localized to the lower right abdomen, first appeared on July 20. During the succeeding ten days, both the staining and the pain persisted intermittently. The only finding disclosed by examination was a smooth, tense, oval mass to the right of a softened, normally-proportioned uterus. The mass was the size of a walnut and moderately tender. A diagnostic curettage revealed the uterine depth to be 8.0 cm., and recovered a moderate quantity of smooth endometrium. An immediate laparotomy uncovered the presence of a lutein cyst of the right ovary which was resected. The histologic study of the endometrium showed a well-developed progestational tissue with several areas suggesting decidual change but no chorionic villi (Fig. 6). The excised luteal tissue was relatively well preserved.

The dubious significance of decidual changes without chorionic villi in the endometrium, when found in a patient suspected of having either an extrauterine gestation or merely a persistent corpus luteum, is further lessened by the possibility of an earlier complete abortion of an

intrauterine pregnancy. In such an instance, termed "occult pregnancy" by Robert Meyer,<sup>11</sup> the conceptus is allegedly expelled completely, leaving no trace of chorionic villi. While it is possible that such an abortion might occur without leaving macroscopically recognizable remnants of fetal tissue, it is hardly conceivable that a few chorionic villi would not be visible microscopically. This is of some importance clinically, because, in performing a diagnostic curettage to exclude the presence of an intrauterine pregnancy in a patient suspected of having a tubal abortion, the gynecologist rarely employs the frozen section method of immediate microscopy. If the curettings are scanty and appear, on macroscopic inspection, to be free from chorionic elements, laparotomy usually follows. That the chance of error, under such circumstances, is not merely an academic problem but a very practical one, is illustrated by the following case history:

CASE 6.—S. C. (Mount Sinai Hospital, No. 106696), a tertipara, aged 24 years, who normally had a menstrual cycle of twenty-eight-day

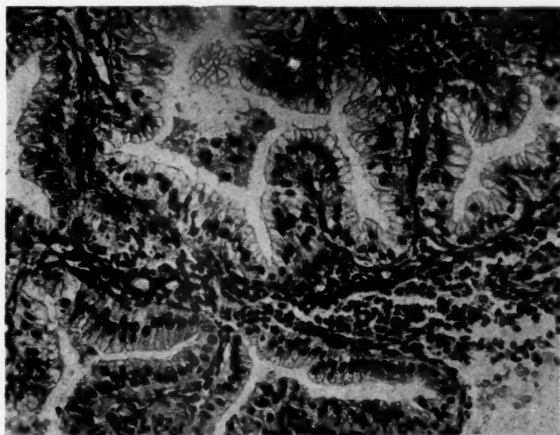


Fig. 6.—Photomicrograph of specimen of endometrium (Case 5), showing the pseudo-decidual character of the glands.  $\times 250$ .

intervals and a four-day flow, was admitted to the hospital on April 10, 1937. She stated that her last period had begun on February 24 and had been unusually scanty, lasting only a few hours, and that the period expected on March 24 had been missed. Irregular uterine bleeding, accompanied by brief spells of vertigo and by intermittent, sharp pain in the left lower abdomen, had begun on April 5. On April 10, examination showed a smooth, tender, doughy, thumb-sized tumor of the left adnexa. There were no signs suggestive of an abortion. Diagnostic curettage revealed a uterine depth of 8.0 cm., and a small quantity of endometrium which was grossly interpreted as being "normal." An immediate laparotomy revealed only a tense, blood-filled corpus luteum in the left ovary which was resected. On histologic study, the curettings showed decidua and chorionic villi, and the excised ovarian tissue a well-vascularized corpus luteum.

In a recent communication describing the endometrium of a patient proved to have a persistent corpus luteum, Black and his associates<sup>12</sup>

reported the presence of stainable fat globules in the basal portion of the uterine gland cells as being a characteristic feature of a well-developed secretory endometrium. This confirmed the earlier observations of Aschheim<sup>13</sup> who was the first to draw attention to the basal or infranuclear location of the intracellular lipoid substance in the endometrial glands during the premenstrual phase of the cycle. Although the finding of such infranuclear fat droplets may in the future be accepted as an indicator of the response of the endometrium to an adequate supply of progestin, it cannot be looked upon as a criterion of differentiation between a persistent corpus luteum cyst and ectopic gestation. Gillman<sup>14</sup> showed that the basal fat in the gland cells also increased during early pregnancy, suggesting that its appearance is in some manner related to the metabolism of progestin.

*Excretion of Pregnanediol.*—The finding of pregnanediol, the catabolic derivative of progestin, in the urine is considered to be an evidence of the current metabolism of progestin and is interpreted as a signpost of the existence of functioning lutein cells in the ovary.<sup>9</sup> It is to be expected, therefore, that a persistent corpus luteum will be accompanied by an excretion of pregnanediol just as long as the lutein cells function. No information is, however, available concerning the excretion levels of pregnanediol in women proved to have such a functioning corpus luteum cyst. There is, moreover, reason to believe that even if the quantity of pregnanediol excreted by such women were known it would be of little diagnostic value in the presence of signs and symptoms suggesting a tubal gestation. The latter condition, depending for its continued growth on the coexisting corpus luteum of pregnancy, is also accompanied by the excretion of pregnanediol in the urine.<sup>15</sup>

#### MANAGEMENT OF THE PROBLEM

The persistent corpus luteum, simulating ectopic pregnancy, is not encountered often enough to warrant its consideration as a serious problem in differential diagnosis. Even if the preoperative error in diagnosis were more common than it is, the fact that there is no expectant treatment of ectopic pregnancy would not permit surgery to be withheld in many of the instances under discussion. Once the diagnosis of tubal pregnancy is made, the more immediate the surgery the better. When, however, there is some doubt concerning the interpretation of an adnexal mass in association with a history suggesting the presence of either unruptured tubal pregnancy or tubal abortion, conservatism in the form of vigilant observation in a hospital is justified. The period of time to be devoted to such alert watchfulness cannot be dictated by generalities but must be decided for each patient individually.

The histories of the five patients recorded in the foregoing paragraphs pertinently emphasize the probable value of a period of careful observation in the hospital for patients suspected of harboring either a tubal abortion or a corpus luteum cyst. This should be permitted under the watchful eyes of a house staff informed of the diagnostic possibilities.



When, in such a patient, there is an increase in either the objective signs or the subjective symptoms, operation is obligatory. If, on the other hand, the severity of the syndrome under suspicion abates, operation may be held in abeyance until there are definite assurances of the patient's recovery. In occasional instances, needless laparotomy may be avoided by the physician's good judgment and brave patience, two virtues which are fathered only by experience.

#### SUMMARY

1. The history, pathogenesis, and histology of the corpus luteum cyst are briefly reviewed. It is emphasized that, aside from being recognized as a perversion of physiology often attributable to temporary hyperpituitarism, little is known concerning its etiology.

2. The clinical similarity of the corpus luteum cyst and certain types of ectopic pregnancy, an observation credited to Halban, is discussed. It is shown that both conditions may present identical symptoms and pelvic signs, as well as similar laboratory findings.

3. Five patients, each of whom had a corpus luteum cyst preoperatively diagnosed ectopic pregnancy, are cited. The condensed histories and the accompanying illustrations sufficiently exemplify the ample reasons for the diagnostic errors, including the presence of a falsely positive biologic pregnancy test in two instances.

4. The probable physiologic mechanisms of the excessive excretion of gonadotropin (positive Friedman test) and of the deciduallike pattern of the endometrium, both of which are shown to be possible in association with a corpus luteum cyst, are described.

5. It is suggested that even if patients with a suspected adnexal tumor and a history *suggestive* of ectopic gestation were not operated upon immediately but were first carefully observed in a hospital for several days it would be difficult to escape the possibility of an occasional needless abdominal operation.

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2116 SPRUCE STREET

## RENAL AND URETERAL CALCULI IN PREGNANCY\*

### WITH AN ANALYSIS OF TWENTY CASES

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CALCULOUS disease of the urinary tract is an infrequent but significant complication of pregnancy. Although an enormous literature has accumulated on the subject of urolithiasis, it is interesting that, so far as we can ascertain, exclusive investigations of the association of stones with pregnancy have been scant. Crabtree and Prather<sup>1</sup> have included a consideration of this problem in a broad study of urinary tract infection in pregnancy. Interesting isolated cases have occasionally been reported such as that noted by Young and Carver<sup>2</sup> who observed a case of bilateral cystine renal calculi in pregnancy. Incidental mention also is noted, such as Turley's discussion of Allen's<sup>3</sup> paper on fibrin calculi. We have felt, therefore, that an individualized study is indicated of the numerous significant implications regarding the etiology, diagnosis, treatment, and potential complications of this condition.

### ETIOLOGY OF CALCULI IN PREGNANCY

*A. General Considerations.*—The recent studies of Randall<sup>4</sup> have contributed much to our concept of stone formation. Formerly, the etiology of urinary calculi was classified into two groups. The *primary* calculus was the type for the origin of which there could be found no reasonable explanation. Such a patient generally presented himself or herself with a typical clinical picture of renal colic and then later passed a stone. Subsequent inquiry into the history, physical examination, laboratory and roentgenographic reports failed to reveal the pathologic processes underlying this stone formation. This is the type of calculus which Randall and his co-workers showed to be the result of the deposition of calcium salts in nature's attempt to repair damaged tissue in the renal papilla; this plaque acted as a nidus which induced a disturbance in the colloidal balance of the salts in the calcine urine with

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their subsequent crystallization. The *secondary* variety of renal calculi have included those stones for which the etiology could be explained on the basis of some altered physiologic or pathologic causal factors, i.e., nutritional deficiency (vitamin A), hyperparathyroidism, infection superimposed on stasis, etc.

*B. Alterations in Mineral Metabolism During Pregnancy.*—It should be realized from the outset that blood calcium readings are not reliable criteria of the calcium content of the tissues. For example, a calcium deficiency may be present despite normal blood calcium readings. The reason for this is that the calcium reserves in the muscle, bones, and other tissues must be appreciably depleted before a hypocalcemia results. Similarly, Toepfer and Sherman<sup>5</sup> have demonstrated the fact that growth and body calcium economy can be stimulated to higher ranges of activity by liberal increases in the calcium or calcium and phosphorus factors in the diet. The potential importance of this somewhat voluntary control of mineral metabolism becomes readily apparent when it is realized that aberrant metabolic changes in body calcium may occur even during normal pregnancy. Apperman<sup>6</sup> has pointed out that flat calcareous plaques are noted frequently on the maternal surface of the placenta; Frankel showed that these were infiltrations of calcium into the necrotic tissue in the region of the terminal portions of the fastening villi, as well as in the external layer of the decidua serotina. He also refers to Rokitansky's description of "puerperal osteophytes"; these are "irregularly shaped plaques of porous, newly formed bone or osteoid tissue found on the internal surface of the cranial bones."

*C. Urinary Stasis and Infection During Pregnancy.*—Within recent years, it has been clearly shown that more than 85 per cent of pregnant women have demonstrable changes in the ureteral tone and anatomic character of the upper urinary tract. Beginning at the termination of the first trimester, the fundamental contributing factors to this metamorphosis are the pressure exerted by the gravid uterus and the hormonal reorganization associated with pregnancy. The effect is essentially a diminution in the peristaltic tone of the ureter and a dilatation of the calyceal system, pelvis, and ureter. A physiologic hydronephrosis and hydroureter may therefore occur. These changes are both more frequent and more marked on the right side, probably due to the extrinsic force presented by the uterus after it arises out of the true pelvis. The tendency to recession to the normal anatomic and physiologic status commences during the last trimester and is generally achieved at six to eight weeks post partum; the latter depends upon several factors, especially the presence of pyelitis during pregnancy as pointed out by McConnell and Gray.<sup>7</sup> The significance of these alterations in the aqueduct system of the upper urinary tract is that the associated urinary stasis provides a fertile culture media for any potential infection.

The incidence of renal infection in pregnancy and the puerperium has been reported to be fairly uniform (2.58 per cent, Herman and Muckle;<sup>8</sup> 2.4 per cent, Abeshouse, Linas, and Kolman<sup>9</sup>).

Urinary stasis, per se, has been shown not to be the primary responsible requisite for the formation of urinary calculi. Infection, however, superimposed on long standing stasis may be influential in calculous formation.

*D. Endocrine Factors.*—Any direct causal relationship between urolithiasis and endocrine factors which are at operation during pregnancy still remains to be worked out. In this connection, it is interesting to note the findings of Burns and Schenken<sup>10</sup> who treated male mice with estrogens. They report an appreciably higher incidence of urinary calculi appearing at an earlier age in the treated (33.1 per cent) than in the untreated (4.1 per cent) animals.

When the changes in the mineral metabolism are considered in relation to stasis and infection, it is remarkable that a greater incidence of urolithiasis is not observed in pregnancy.

#### ANALYSIS OF CASES

The present communication is a critical analysis of 20 patients who were found to have renal or ureteral calculi during pregnancy. The group includes 8 patients admitted to the Chicago Lying-in Hospital during the thirty-month period ending July, 1935, the data of which were presented by one of us (R. A.) before a sectional meeting of the American College of Surgeons, together with 12 cases observed at the Louisiana Charity Hospital in New Orleans in the eighteen-month period ending Oct. 1, 1941. This series does not include any instance in which the stone was not definitely diagnosed or any cases in which gestation was not proved. Bladder stones were also excluded.

*Incidence.*—During the period of eighteen months from which this study was made, 82,034 patients (35,701 males and 46,333 females) were admitted to the Charity Hospital of Louisiana at New Orleans. Of this number, 156 patients were discharged with the final diagnosis of either renal or ureteral calculi, a general incidence of 1:525. These were divided according to sex distribution into 111 males and 45 females (ratio 2.5 to 1). This compares favorably with the findings of Bumpus and Scholl at the Mayo Clinic (2.1 to 1). The incidence in the nonpregnant females was 1:1,100. In this same period of time, 9,882 women were admitted to the white and colored obstetric services of Charity Hospital. Twelve proved cases of renal or ureteral calculi were noted in this group, an incidence of 1:820. The Chicago Lying-in Hospital incidence was 1:900. The combined incidence of renal and ureteral calculi in pregnant patients at the Charity Hospital of Louisiana and the Chicago Lying-in Hospital was 1:852.

From the foregoing, it appears that the frequency of calculous disease of the upper urinary tract associated with pregnancy (1:852) is somewhat greater than in nonpregnant women (1:1,100) but not as



great as in the male (1:320). Unfortunately, we have no comparable statistics from other obstetric clinics.

We do not believe, however, that an incidence presently reported represents the true incidence of lithiasis in pregnancy. More serious attempts at diagnosis would undoubtedly reveal a far greater number of cases. These cases have remained undiagnosed in the past, because adequate diagnostic methods were not employed.

The greater relative incidence of pyelonephritis of pregnancy frequently overshadows the consideration of renal and ureteral calculi. The possibility of stone often does not enter the pale of clinical impression until the patient fails to improve with the numerous agents prescribed to combat infection. Finally, a roentgenogram is made and a calculus is observed in the kidney or ureter or both.

*Race, Age, and Parity.*—Racial comparison is possible only in the 12 cases from Charity Hospital, of which 9 were white and 3 colored patients. The proportional racial distribution is actually greater than three to one, because during the period in which these cases occurred the relative distribution of white and colored obstetric admissions to the hospital was 33 to 67. The reason for this very considerable predilection for the white race is not clear, but it furnishes still another example of the marked variation in medical reaction between the two races.

The age range in the 20 cases was 19 to 43 years, and the average age was 28 years. Although there was a definite preponderance of incidence in the third decade (13 cases) as compared with the older age groups (6 cases), this difference could not be regarded as significant in such a small series.

In regard to the factor of parity, the multiparas (14 cases) exceeded the primiparas (6 cases). Twelve patients, 60 per cent, had had three or more pregnancies, and the average parity was 3.8. In the light of the etiology of urinary calculi previously described, these figures may be regarded as logical findings, inasmuch as pyelectasis and ureterectasis and potential infection are more frequent in women who have had several pregnancies. It is interesting to note in connection with this point, however, that the incidence of calculous disease was no higher in women who had numerous pregnancies as compared with those individuals who had relatively fewer pregnancies. It is not felt, however, that a definite conclusion can be formulated in this paper regarding the relation between the degree of multiparity and incidence of renal and ureteral calculi.

*Duration of Gestation.*—In one case the diagnosis was not established until the second post-partum day; the period of gestation in the others varied from six to forty weeks, the average was twenty-four weeks. Although the range is great it is perhaps significant that 50 per cent of the cases were less than midterm and that symptoms had persisted for several months in most of the cases who remained undiagnosed until late in pregnancy.

*Clinical Features.*—The predominant findings in the descending order of their incidence were costovertebral angle pain and tenderness, abdominal pain and tenderness, fever, pyuria and hematuria, and nausea and vomiting. Less frequently encountered findings were frequency of urination, burning on urination, chills, and muscle spasm. In one case a palpable mass could be demonstrated.

Pain was present in all cases and was usually the chief complaint for which the patients sought relief. The pain varied in intensity but



usually was a constant dull ache in the costovertebral angle of the involved side. Twelve of the patients had attacks of renal colic, but only three suffered excruciating pain. None of the patients had had a previous diagnosis of urinary stone although one had had several attacks of colic before she became pregnant, and a diseased gall bladder had been suspected.

The duration of symptoms also showed great variation. The average patient had experienced complaints for a period of about eight weeks, but some had had symptoms for as long as six months while others had been ill for only one week. The clinical picture usually began with symptoms suggestive of pyelitis but the patient often did not seek

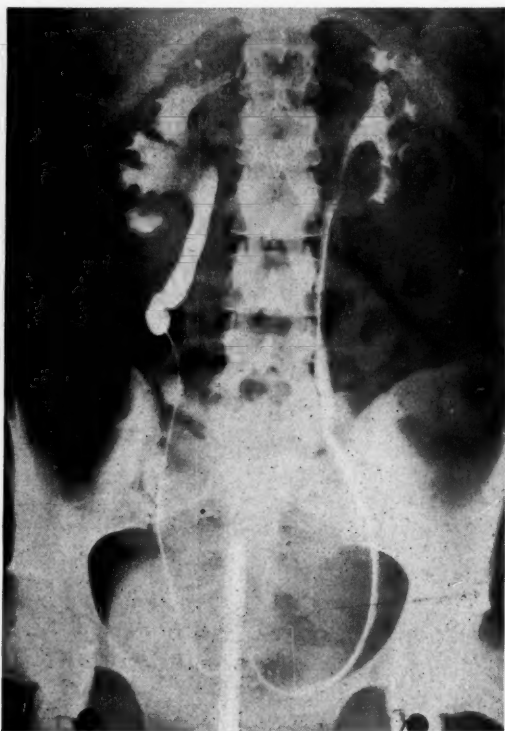


Fig. 1.—E. M. (L-41-46439), 31 years old, white female, gravida iii, was admitted to Hospital on second post-partum day with high fever, chills, and severe pain in right costovertebral angle and right lower quadrant. KUB, large right ureteral calculus and hydronephrosis. Ureterolithotomy performed. Uneventful convalescence.

relief until pain was a predominant feature. As we have stated previously, it is of interest to note that medical consultation was delayed until late in pregnancy in a number of cases, although symptoms had existed since the first trimester.

No unusual or unexpected observations were obtained from the laboratory studies. There was no appreciable azotemia except in three cases (urea nitrogen: 42, 26, and 25 mg. per cent). Thirteen patients had notable amounts of microscopic pyuria and 12 had considerable microscopic hematuria, but only 3 cases had gross hematuria. *Escherichia coli*, staphylococci and streptococci were found on smear and culture of the urine.

The calculi were located in the kidney in 11 cases, in the ureter in 6, in both kidneys in 1, in both ureters in 1, and in both kidneys and both ureters in 1 case. Stones were found on the right side in 12 cases, on the left side in 5, and on both sides in 3 cases. The marked preponderance of stone on the right side corresponds to the increased incidence of pyelitis on that side, and both may be due to the fact that a more marked physiologic dilatation occurs in the right ureter and kidney pelvis than on the left side. It is possible that the changes may be ascribed to the shortened right ureter, its difference in relation to the large iliac and uterine vessels or to dextrorotation of the uterus; all of which tend to increase angulation and occlusion of the ureter.

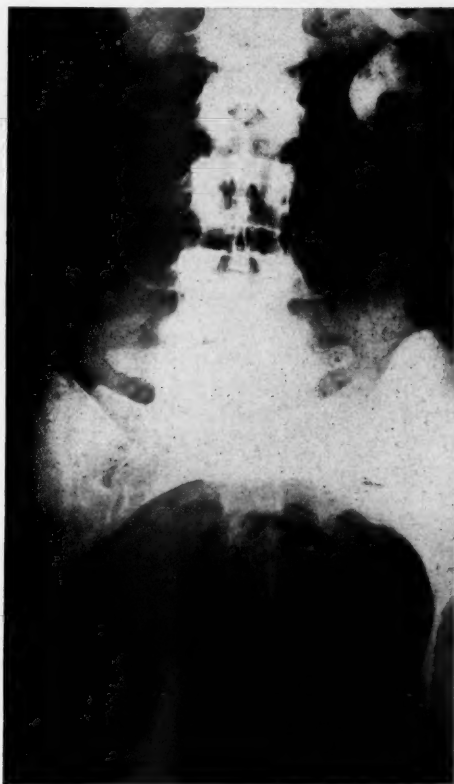


Fig. 2.—M. M. (L-41-45543), 22 years old, white female, primigravida, was admitted to hospital in the fifth month of gestation, complaining of right costovertebral angle pain, urinary frequency and hematuria of three months' duration. *KUB*, right staghorn calculus. Nephrectomy. Uneventful convalescence.

The site of predilection seemed to be in the uteropelvic junction or in the terminal one-third of the ureter, where it occurred in all 20 cases. A single stone was found in 15 of the 17 cases in which one site only was involved.

#### DIAGNOSIS

The differential diagnosis of calculous disease in pregnancy offers considerable difficulty at times and the percentage of error is high.

This is not unexpected inasmuch as the symptoms and findings closely simulate those of other diseases. In this series only five of the 20 cases were diagnosed correctly on the strength of the clinical picture on admission. In 12 cases, 60 per cent, the tentative diagnosis of pyelitis or pyelonephritis of pregnancy was made; two cases were diagnosed as possible appendicitis. Acute salpingitis, threatened abortion and ectopic pregnancy were also included in some of the clinical impressions.

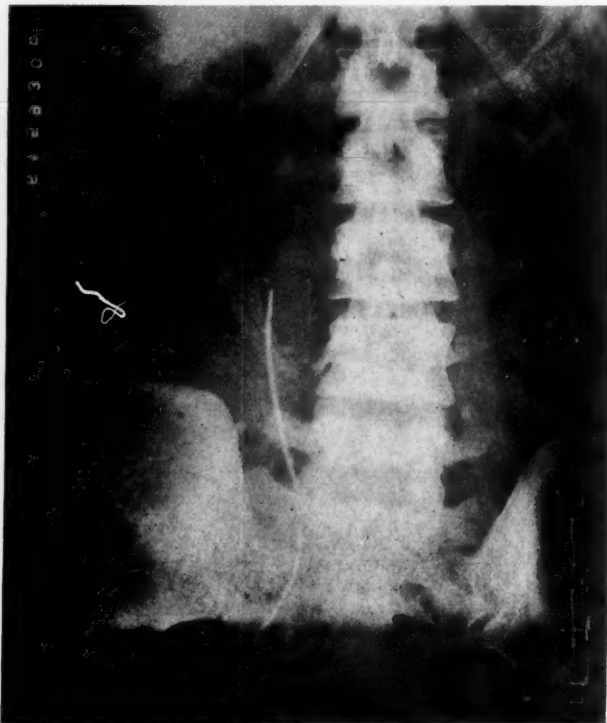


Fig. 3.—I. A. (T-41-48509), 38 years old, white female, gravida x. Diagnosis on admission: pyelonephritis with block, pregnancy (26 weeks). Further study revealed a right renal calculus. Nephrostomy and nephrolithotomy were performed. Premature infant was born three days later, and died on eighth day. Patient recovered after a stormy convalescence.

There are five avenues of approach to the determination of the presence of urinary calculi:

1. History
2. Physical examination
3. Laboratory studies
4. Cystoscopy
5. Roentgenographic observations

There is usually a history of pain that commences posteriorly over the affected kidney or ureter and radiates around the loin to the labia or lower abdominal quadrant on the same side. Occasionally, the pain may begin in the anterior upper abdominal quadrant of the affected side. The pain varies from a severe lancinating type that may be suf-

ficiently marked to produce prostration to a persistent, dull aching pain especially noted in the chronic cases. These attacks of pain are often associated with nausea and vomiting. A history of hematuria, pyuria, and passage of sand, gravel, or tiny stones is helpful in suggesting the diagnosis. Fever and chills are present as a rule only in the presence of infection.

On physical examination, tenderness over the costovertebral angle may frequently be elicited. Tenderness can also be noted on palpating the kidney. Muscle spasm is not a consistent sign. The kidney may be enlarged due to a persistent block with subsequent hydronephrosis.

Examination of the urine will reveal the presence of red and white blood cells and a variable degree of albuminuria, depending on the amount of blood present in the urine. It is important to remember that there may be no pathognomonic urinary findings in the presence of a complete block.

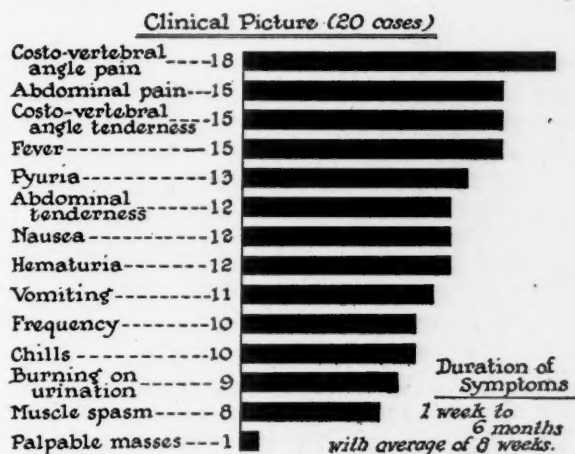


Fig. 4.

Cystoscopic examination can be of inestimable value. Bloody or purulent urine may be noted, being ejected from the ureteric orifice on the involved side. Block and spasm, when encountered while attempting to introduce a catheter up the ureter, are significant in suggesting the presence of a stone.

Three forms of roentgenographic study are available for diagnostic purposes, namely, a plain roentgenograph of the urinary tract, an excretory urogram, and a retrograde pyelogram. The first two procedures do not require cystoscopy and are often preferred for that reason.

#### TREATMENT

In this series, one or more cystoscopic examinations were performed on each of the 20 patients. The procedure was done once in 14 cases, twice in 4 cases, and three times in 2 cases. Cystoscopic manipulations

were successful in removing the stones in 5 cases, and in 6 additional cases the stones were passed spontaneously after intervals of from one day to five months following cystoscopy.

Nine patients were submitted to major surgical procedures which included ureterolithotomy (3 cases); nephrectomy (2 cases); nephrolithotomy, pyelolithotomy, nephrostomy, and combined ureterolithotomy and nephrostomy (each one case). Six operations were performed during pregnancy; while in three cases, surgical intervention was deferred until after delivery. One of the latter cases required nephrectomy, and it appeared likely that earlier intervention possibly would have spared the kidney.

Specific chemotherapy was employed whenever possible, especially in the administration of the sulfonamides and mandelates. Supportive measures consisted of fluids by mouth, infusions, transfusions, wholesome diets, and pure vitamin principles. Indwelling ureteral catheters were employed to enhance drainage as indicated. Labor was induced once.

The only specific suggestion that is suitable in governing the treatment of urolithiasis in pregnancy is that each case requires individual appraisal and judgment. One must not lose sight of the fact that the approach to the problem must be directed toward a threefold objective, namely, preservation of the life and well-being of the mother, the fetus, and the kidney on the affected side. Toward this end, a few basic criteria should be kept in mind. Briefly, these may be outlined as follows:

1. The size of the stone
2. The location of the stone
3. The presence of infection
4. The duration of symptoms
5. The efficiency of renal function on the unaffected side
6. The status of the patient (toxemia, azotemia, etc.)
7. The period of gestation

A routine that allows wide latitude of variations and modifications is suggested, based on the assumption that the diagnosis of urinary calculi has already been made. In the Charity Hospital of Louisiana, a similar systematic follow-up is conducted in close cooperation by the obstetric and urologic services.

#### I. SYSTEMIC CARE

##### A. *Fluids.*—

1. Fluids are forced by mouth (3,000 c.c. daily minimum). The intake and output should be carefully charted by the nursing staff. During the summer months or if the patient has a tendency to perspire profusely, an extra 1,000 c.c. of fluid is given.

2. In the presence of marked vomiting or when the patient refuses to take adequate fluids by mouth, 3,000 c.c. of fluid are given by infusion distributed as follows: 1,000 c.c. of 10 per cent dextrose in normal saline; and 2,000 c.c. of 10 per cent dextrose in distilled water.

3. Blood transfusions as necessary to combat anemia.



*B. Urinary Antiseptics.*—These are prescribed according to the type of organisms found on smear and culture of urine.

1. Staphylococci: sulfathiazole, sulfadiazine, neoarsphenamine.
2. Streptococci: sulfanilamide, sulfadiazine.
3. Bacillary infections: mandelates.

*C. Sedation.*—It is important to keep the patient comfortable, but it is equally essential not to maintain the patient in a stuporous state. The choice of hypnotics should be influenced by the fact that these are being administered to a pregnant individual.

*D. Urinary Suppression.*—

1. Diathermy over each kidney for twenty minutes, every four hours.
2. Sucrose (50 per cent), 50 c.c., intravenously, B.I.D.
3. Caffeine sodium benzoate, gr. VISS, T.I.D.
4. Fluids as prescribed above.
5. Ureteral catheterization as indicated.

## II. TREATMENT OF THE OFFENDING CALCULI

*A. Renal Calculi.*—

1. In the absence of infection and complete block, conservative measures are justified. Supportive measures should be sufficient in most instances and specific treatment (nephrolithotomy, nephrectomy, etc.) postponed until a future propitious postpartum date.

2. In the presence of infection, treatment should be aimed at combating this factor (fluids, chemotherapy, etc.). In the presence of a block, it is mandatory that drainage be established by means of an inlying ureteral catheter or even a nephrostomy. Sometimes a small stone will pass spontaneously or with the aid of antispasmodics and catheter manipulation. It should be emphasized that surgical measures should be contemplated if appreciable improvement is not attained by conservative means within a reasonable length of time. This may take the form of nephrolithotomy, pyelolithotomy, or even nephrectomy. Jones<sup>11</sup> has reported a case of pyelonephritis of pregnancy complicating bilateral renal calculi in which a right nephrectomy and left nephrolithotomy were done.

*B. Ureteral Calculi.*—

1. In the absence of infection and complete block, conservative measures are indicated (sedation, antispasmodics, etc.).

2. In the absence of infection, but in the presence of a complete block, the primary consideration is to re-establish drainage. This is accomplished by means of introducing a ureteral catheter proximal to the site of obstruction.

After drainage is established, an attempt should be made to dislodge the calculus by means of ureteral manipulation, antispasmodics, etc. If it is not possible to get by the site of obstruction with a catheter after a reasonable number of trials, a ureterolithotomy should be contemplated. It is also important to prescribe prophylactic measures in anticipation of any potential infection.

3. In the presence of infection, drainage must be assured. Specific measures must be taken against the infection and the calculus should ultimately be removed. Surgical measures should be performed as indicated.

It is needless to analyze each of these points in definite detail. The significance of most of them is self-evident and the numerous varia-

tions encountered need not be completely enumerated in this paper. The final decision will remain within the province of discussion and judgment of the obstetrician and urologist acting in mutual collaboration.

A few salient points should be borne in mind in connection with the above routine. For instance, a small stone, which ordinarily would pass without any appreciable difficulty might become imbedded with stubborn resistance at any of the several normal sites of constriction in the ureter. The complete obstruction that might result in this situation is fraught with no less danger than a much larger calculous formation in the kidney. It is more encouraging to deal with a stone that has passed half way down the ureter than one which meets an impasse at the ureteropelvic junction; in the former case, we have more reasonable assurance that the stone might pass spontaneously or with the aid of antispasmodic drugs and catheter manipulation.

There may be fortunate occasions during which one can afford to temporize such as when drainage can be re-established by means of an inlying ureteral catheter, infection is controlled, and excellent renal function is present on the unaffected side. At other times, surgical interference may be indicated, such as in the case of an uncontrolled infected hydronephrosis complicating calculous obstruction. When surgical intervention becomes the treatment of choice, pregnancy and parity should be secondary considerations.

Frequently, especially early in pregnancy, there is a reluctance to subject the pregnant patient to cystoscopic examination and ureteral catheter manipulations for fear of exciting abortion or premature labor. Our own experience has led us to conclude that this attitude is not justifiable. We have found that these urologic procedures can be performed as frequently as indicated, providing that proper sedation and utmost gentleness are put to use. In connection with this point, the following findings are of interest. In the interval between July, 1940, and July, 1941, 106 patients with pyelonephritis of pregnancy were admitted to the Charity Hospital. Of this number, 35 patients received cystoscopic examinations. Two of this group of patients, both near term, went into labor and delivered normal viable babies within twenty-four hours of the cystoscopy. It would be difficult to evaluate the part played by the urologic procedure in stimulating labor. In this series there were no other instances of premature labor initiated by the cystoscopic procedure, and there were no accidents or untoward effects.

#### RESULTS

There was no maternal mortality. There were 3 fetal deaths, an uncorrected fetal mortality of 15 per cent. L. L., six weeks pregnant, required a pyelolithotomy; abortion occurred on the seventh postpartum day. N. A., twenty weeks pregnant, passed a ureteral stone

following cystoscopy, but aborted forty-eight hours later. I. A., eight months pregnant, required a nephrostomy and nephrolithotomy and delivered a premature baby who died eight days later. In three other cases premature delivery occurred, but the infants survived.

#### SUMMARY AND CONCLUSIONS

1. Twenty cases of nephrolithiasis or ureterolithiasis complicating pregnancy are reported, with no maternal deaths and a gross fetal mortality of 15 per cent. In this series the incidence of urolithiasis was one in every 852 pregnancies, which is about twice the frequency found in nonpregnant females of the same age group. Only 3 occurred in colored patients.

2. Race, sex, age, endocrine factors, and vitamin and mineral metabolism play a part in stone formation, but the chief causes, apparently, are stasis and infection. Pregnant women undoubtedly present a number of cardinal requisites for calculous formation but these are counteracted in part by the fact that pregnancy is of relatively short duration.

3. The clinical features of urolithiasis associated with pregnancy are briefly discussed. The diagnosis is dependent upon the demonstration of the stone, which is most readily identified by cystoscopic and roentgenologic examinations.

4. Pyelonephritis is easily confused with urolithiasis during pregnancy, and 12 of 20 cases were so diagnosed. The close clinical similarity of the two conditions is responsible for the error.

5. Lumbar pain and tenderness, fever, and nausea and vomiting were the outstanding symptoms; the chief laboratory findings were pyuria and hematuria.

6. In general, the management of urolithiasis during pregnancy depends upon the individual case, and a high degree of obstetric and urologic cooperation is demanded. If the condition is latent or the symptoms not severe, conservative therapeutic measures are preferable. After parturition the stone should be removed. In those cases in which symptoms are severe, operation is mandatory. In most instances the pregnancy will continue without interruption. Urethral passage of the stone occurred in 11 cases while 9 cases required surgical intervention.

7. While cystoscopy during pregnancy should not be considered an innocuous procedure, evidence is given in support of the view that its hazards do not contraindicate its use in properly selected cases.

8. Urolithiasis during pregnancy is a condition which demands general recognition and further study. Only by these means will the true incidence be established, the etiologic factors peculiar to pregnancy be determined, and improved methods of diagnosis and treatment be evolved.

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## ADDENDUM

Since this manuscript was prepared, two additional cases of ureterolithiasis associated with pregnancy have been observed in the Charity Hospital at New Orleans. Spontaneous expulsion occurred in one instance, while in the other the stone was removed by means of cystoscopic manipulation. The patients were white multiparas in the second trimester of pregnancy, and the gestations were undisturbed.

## TOXIC MANIFESTATIONS IN THE NEWBORN INFANT FOLLOWING PLACENTAL TRANSMISSION OF SULFANILAMIDE

WITH A REPORT OF 2 CASES SIMULATING ERYTHROBLASTOSIS FETALIS

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THE purpose of the present communication is to describe a hitherto unreported mode of sulfonamide toxicity and to add a further note of caution against the indiscriminate use of the sulfonamides, specifically, during pregnancy. This has been occasioned by the observation of two cases of sulfanilamide toxicity in the newborn, one fatal, following the administration of the drug to the pregnant mother.

In 1937, Marshall, Emerson, and Cutting<sup>1</sup> demonstrated that sulfanilamide is rapidly distributed throughout the body and may be found in somewhat varying concentrations in the different tissues of the body soon after it is administered. Shortly thereafter, it was shown that the drug passes readily through the placental barrier<sup>2</sup> and may be found in the fetus soon after administration to the mother, equilibrium between the concentrations in the fetal and maternal blood being reached in three to five hours. This is true for both man and animal (rabbit, rat). The ready passage of the drug through the placenta apparently does not vary with the stage of pregnancy, thus differing from the passage of neoarsphenamine.<sup>3</sup> There is evidence to show that sulfapyridine, at least, of the other members of the sulfonamide group of drugs, also passes freely through the placenta.<sup>4</sup> The extensive use of sulfanilamide and other sulfonamides during pregnancy for various complicating



intercurrent infections therefore raises the question of the possible deleterious effects of these drugs upon the fetus.

There are only meager clinical reports on the effects of placenta-transmitted sulfanilamide. In a series of 17 cases, Barker<sup>2b</sup> found no complications in any of the infants. However, the doses given were small, varying from 15 to 80 gr. given to the mothers at term, 0 to 40 hours before delivery. Likewise, Speert<sup>2c</sup> found no ill effects on the infants in 15 cases of administration of sulfanilamide to pregnant women. Here again the doses were small and given at term, a single dose of 0.06 Gm. per kilo of body weight one to thirty-eight hours before delivery. In the experimental field, Speert,<sup>4</sup> working with rats, found that prolonged administration of sulfanilamide, in amounts well within the limits of safety to the adult animal, produced markedly injurious effects on the fetus, as demonstrated by increased intrauterine and postnatal mortality, decreased litter size, decreased birth weight, and striking selective stunting among the offspring. As Speert remarks, the selectiveness of the stunting suggests a possible individual idiosyncrasy or sensitization to the drug, a point which will be considered again in the discussion.

It would appear, then, from Speert's observations, that the prolonged administration, during pregnancy, of sulfanilamide and, without doubt, the other sulfonamide drugs, is not without the possibility of danger to the fetus or its postnatal development. Nor does the absence of ill effects on the infants in the above-mentioned clinical reports militate against the possibility of the occurrence of occasional serious toxic effects of the drug in the newborn due to individual hypersensitivity, just as they occur only occasionally in patients to whom the sulfonamides are administered directly. We consider it timely, therefore, to present a case of fatal acute yellow atrophy of the liver in the newborn due to sulfanilamide transmitted from mother to fetus through the placenta, and a case of acute hemolytic anemia in the newborn, with recovery, in which this same mechanism seems probable. We have been unable to find any similar recorded observations. These cases are of further interest, in that, because of the clinical and hematologic features, they were both, apparently erroneously, diagnosed as erythroblastosis fetalis.

CASE 1.—M. W., an 18-year-old primigravida, colored female, was admitted to the Sydenham Hospital Oct. 22, 1940, with ruptured membranes. Other details of the history, physical examination, and laboratory data were not significant, except that the Kahn, Kline, and Wassermann tests were negative. On the second day the temperature rose to 102° F. and on the third to 103.6° F. A diagnosis of infection of the amniotic sac was made, and 15 gr. of sulfanilamide were given every four hours. Seven doses were given, a total of 105 gr. No determinations of blood-level concentration were made. Three hours after the last dose, spontaneous delivery of an apparently normal, healthy female infant took place. On the third day after delivery, the mother's temperature became normal and the subsequent course was uneventful.



The child weighed at birth 4 pounds, 12 ounces and measured 20 inches in length. The color and condition of the infant were good, and physical examination revealed no abnormalities. The temperature was normal for the first three days, but on the fourth day rose to 101.4° F. and, for the first time, the infant appeared icteric and the condition poor. A blood count at this time revealed 13.9 Gm. Hg (82 per cent) per one hundred c.c.; and 3,950,000 erythrocytes, 33,350 leucocytes, and 270,000 platelets per c.mm. Differential smear showed 51 per cent segmented and 20 per cent nonsegmented neutrophilic leucocytes, 2 per cent myelocytes, 22 per cent lymphocytes, and 5 per cent monocytes. The smear also showed polychromasia, and 34 nucleated erythrocytes per 100 leucocytes, megaloblasts predominating. The urine contained a trace of urobilinogen and no bile. The stools were of normal color. The liver and spleen were not palpably enlarged. On the following day, the fifth day of life, a sulfanilamide determination of the blood showed 1.5 mg. per cent, although the child had never been given the drug directly. On October 31, three days after the first count, a second blood count showed 16.5 Gm. Hg, 4,000,000 erythrocytes and 23,950 leucocytes with 51 per cent segmented and 18 per cent nonsegmented neutrophils, 24 per cent lymphocytes, and 7 per cent monocytes; and there were 27 nucleated erythrocytes per 100 leucocytes. The jaundice increased and the child's condition became increasingly poor. She vomited frequently, and became cyanotic at intervals. Except on 2 occasions and terminally, the temperature remained normal. Death occurred a little more than eight days after birth. The final clinical diagnosis was erythroblastosis fetalis.

*Necropsy.—Gross Findings:* The body was that of a poorly nourished, colored female infant, 2,100 Gm. in weight and 48 cm. in length. The sclerae were distinctly icteric, and there was an icteric tint to the rather light-colored skin. Except for a focal, pinhead-sized hemorrhage in the left cerebellum, the macroscopic pathologic changes were confined to the liver. The liver weighed approximately 100 Gm., and was of normal or somewhat diminished size, and of soft consistency. The liver parenchyma was of a mottled brownish-red to yellow color and peppered throughout with innumerable small grayish white dots. The portal and hepatic vessels, gall bladder and bile ducts were normal. The spleen weighed 10 Gm., and was essentially of normal size and gross appearance, and firm in consistency. The umbilical stump was clean. There was no kernicterus of the basal nuclei of the brain.

*Microscopic Findings.—Liver:* Microscopic sections of all portions of the liver showed an extraordinary picture of extensive necrosis with only scattered, irregular islands of intact parenchyma which had no constant relation to the lobular architecture. The preserved liver cells were, for the most part, either histologically normal or showed mild fatty change; they merged either abruptly, or gradually with intervening more or less degenerated cells, with the areas of necrotic parenchyma. Both in the areas of intact parenchyma, including the portal connective tissue, as well as in the degenerated and necrotic areas, there was a complete absence of either intrasinusoidal or interstitial extramedullary hematopoiesis. The necrotic areas constituted the major portion of all sections. They consisted in part of remaining shadows of necrotic "ghost" liver cells and pyknotic nuclear material, and in part of areas where the necrotic liver parenchyma had completely disappeared, leaving only the congested sinusoids and reticulum framework of the liver. No evidence

of any inflammatory reaction was present, and careful search with special stains failed to reveal any bacteria or spirochetes. *Adrenals:* Sections of both adrenals showed numerous focal areas of necrosis of the cortex, very similar in appearance to those in the liver but smaller and less extensive, alternating with completely intact parenchyma. Here also there was a complete absence of bacteria, inflammatory reaction,

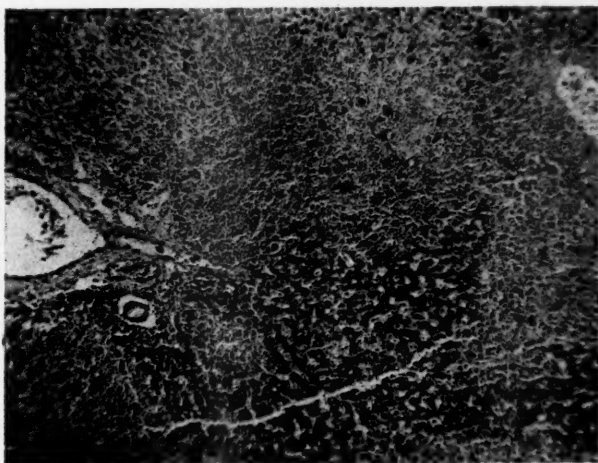


Fig. 1.—(Case 1.) Photomicrograph of liver showing extensive degeneration and necrosis of parenchyma. Low power ( $\times 56$ ).



Fig. 2.—(Case 1.) Higher magnification showing details of the liver necrosis and absence of hematopoiesis. ( $\times 96$ .)

or hematopoiesis. *Spleen:* Sections showed a normal architecture and structure. The Malpighian corpuscles were of normal size and number. Within the red pulp were scattered, microscopic foci of necrobiosis. There was no evidence of the extramedullary hematopoiesis or myeloid metaplasia, or picture of arrested development of the spleen characteristic of erythroblastosis fetalis.<sup>5</sup> No noteworthy hemosiderosis was present.

Histologic study of the other organs included a section of the lung showing 2 microscopic foci of necrobiosis of the alveolar walls, a section of the left cerebellum showing a small, focal hemorrhage with early perifocal cellular reaction, and sections of the kidney showing mild tubular degeneration. Sections of the bone marrow, studied in detail, showed no significant changes. Sections of the umbilicus and umbilical veins up to the liver showed no evidence of infection.

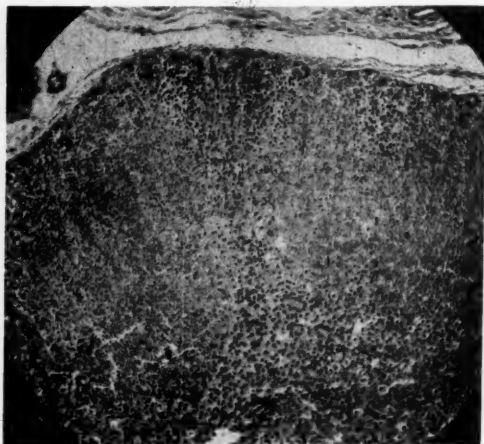


Fig. 3.—(Case 1.) Photomicrograph of adrenal showing areas of cortical necrosis. ( $\times 60$ .)

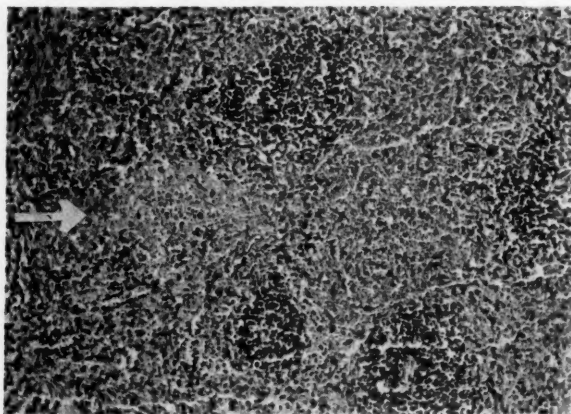


Fig. 4.—(Case 1.) Photomicrograph of spleen showing normal pulp and follicle structure and absence of extramedullary hematopoiesis or myeloid metaplasia. Arrow points to focal area of necrobiosis. ( $\times 96$ .)

#### COMMENT

In the absence of any evidence of bacterial infection, congenital syphilis, or congenital obliteration of the bile ducts, the combination of jaundice and the erythroblastotic blood picture naturally suggested the diagnosis that was made of erythroblastosis fetalis, although, in retro-

spect, the absence of anemia, hepatomegaly and splenomegaly, the onset of jaundice only on the fourth day, and the fact that this child represented the first pregnancy of this mother speak against the diagnosis. In view of the recent studies of Levine and his co-workers<sup>9</sup> on the etiology and pathogenesis of erythroblastosis fetalis, it is unfortunate that the parents are not now available to determine their Rh status. However, the pathologic findings, especially in the liver and spleen, are sufficient to negate this diagnosis and to show instead that the case is one of acute yellow atrophy of the liver associated with focal necroses of the adrenals, spleen, and lung, in which there appears full justification for attributing these changes to the sulfanilamide that was demonstrated in the infant's blood on the fifth day of life and which had been transmitted from mother to infant through the placenta.

CASE 2.—M. C., a full-term, spontaneously delivered, three-and-one-half-week-old, white female infant, was admitted to the Sydenham Hospital, Sept. 13, 1940, because of marked pallor since birth and the development of a faintly yellow color in the skin. The child had otherwise been perfectly normal, and one sibling five years old was living and well. It was subsequently learned that the mother had taken 57 tablets of sulfanilamide shortly before delivery, although unfortunately the exact details concerning this medication and the nature of the infection for which the drug was given were not recorded on the infant's chart.

On admission, the blood count showed 6.8 Gm. Hg per 100 c.c. (40 per cent) and 2,020,000 erythrocytes and 8,600 leucocytes per c.mm., with 10 per cent nonsegmented and 21 per cent segmented neutrophils, 1 per cent eosinophils, 60 per cent lymphocytes, and 8 per cent monocytes; there were 41 nucleated erythrocytes per 100 leucocytes. Polychromasia, basophilic stippling, and microcytosis were noted. Reticulocytes were 9.3 per cent. A second count, three days later, showed an essentially similar picture as did a third, two days later, except that the hemoglobin had fallen to 5.6 Gm. and the erythrocytes to 1,590,000. The liver and spleen were moderately enlarged. The indirect van den Bergh gave a result of 1.6 mg. per cent of bilirubin; the direct was negative. The clinical diagnosis was erythroblastosis fetalis.

The child remained in the hospital for two months and was treated by diet with iron and liver, and received 4 small transfusions totaling 215 c.c. of citrated blood. On this treatment the infant made a complete recovery, successive blood counts showing a progressive disappearance of the nucleated erythrocytes, the reticulocytes dropping to 1.2 per cent on Nov. 12, 1940, and the hemoglobin rising to 11.7 Gm.

#### COMMENT

Except for absence of the usual leucocytosis and "shift to the left" of the leucocytes, the clinical and hematologic features in this case justify the diagnosis that was made originally of erythroblastosis fetalis. However, the excellent result effected by a treatment consisting chiefly of 4 small transfusions complemented by small amounts of liver and iron cast some doubt on the correctness of this diagnosis, and, after the



neeropsy in the first case, the clinical and hematologic similarities of the two cases were recalled; it was at this time that we felt that this was possibly not a case of erythroblastosis fetalis, but, from the lesson drawn in the first case, might well represent a severe hemolytic anemia due to placenta-transmitted sulfanilamide and such as is not infrequently found to complicate the direct administration of sulfanilamide. It is unfortunate that the exact details of the amounts and time of the administration of the sulfanilamide to the mother, especially in relation to the time of delivery, are not available, and that no sulfanilamide determination was done on the infant. It is unlikely in any case that the latter procedure would have given any information inasmuch as the child was not seen in the hospital until three and one-half weeks after birth.

#### DISCUSSION

The clinical and especially the pathologic evidence in the first case is clearly sufficient to warrant discarding the diagnosis of erythroblastosis fetalis and attributing the fatal liver damage to sulfanilamide transmitted from the mother to fetus through the placenta. The data in the second case are, unfortunately, not so conclusive, but here, also, there appears to be good reason to doubt the diagnosis of erythroblastosis fetalis and consider a similar mechanism responsible for the development of the anemia. This is all the more likely in view of the fact that liver damage, acute hemolytic anemia, and reticulocytosis (as was present in Case 2) have been noted not infrequently following direct therapy with sulfanilamide. It is of interest that the placenta-transmitted sulfanilamide should stimulate such a hematic reaction in these infants, for which two factors, at least, are probably responsible. As shown by Watson and Spink,<sup>7</sup> sulfanilamide causes an acceleration of hemoglobin metabolism characterized by an increase in fecal urobilinogen and a varying increase in reticulocyte percentage, increased hemolysis, and a disturbance in hemoglobin formation as evidenced by the occurrence of macrocytic or normocytic, mildly hypochromic anemia. In addition, it is not unusual for the rather labile hematopoietic process in the newborn to react in this manner to a variety of stimuli, such as infections, anemia, etc., even in the absence of true erythroblastosis fetalis.

The evidence of these two cases demonstrates that the free passage of sulfanilamide through the placenta when given to the pregnant mother exposes the fetus or newborn infant to the hazards of the possible toxic effects of the drug. Inasmuch as sulfapyridine also has been shown to pass through the placenta as freely as sulfanilamide, this danger must be considered possible for all of the sulfonamides. This is pointed out, not with any intention of discouraging the use of these extremely valuable therapeutic agents, but to re-emphasize the caution with which they must be used.



In regard to sulfanilamide specifically, the most grave of the toxic effects include acute hemolytic anemia, leucopenia and neutropenia, and more or less severe or even fatal liver damage. The last, contrary to the supposition of many, is by no means uncommon, and was the obvious cause of death in Case 1.

Watson and Spink<sup>7</sup> observed 16 cases of distinct or marked jaundice in 110 patients receiving sulfanilamide, although the latter figure did not include all the patients receiving the drug, making the actual incidence of the complication uncertain. Long, Bliss, and Feinstone<sup>8</sup> report 2 cases of jaundice without anemia clearing rapidly on withdrawal of the drug among 307 adults treated. Other cases of liver damage with recovery have been reported by Hageman and Blake,<sup>9</sup> Saphirstein,<sup>10</sup> Garvin,<sup>11</sup> Silver and Elliott,<sup>12</sup> Fitzgibbon and Silver,<sup>13</sup> Greene and Hotz,<sup>14</sup> and Spring and Bernstein;<sup>15</sup> fatal cases by Garvin,<sup>11</sup> Bannick, Brown, and Foster,<sup>16</sup> and Ottenberg;<sup>17</sup> and fatal cases with post-mortem demonstration of liver damage by Greene and Hotz,<sup>14</sup> Tragerman and Goto,<sup>18</sup> Russell<sup>19</sup> (neoprontosil also given), Berger and Applebaum,<sup>20</sup> and Cline.<sup>21</sup> In the last 3 reports, as also in our Case 1, the liver changes described were of the order of an acute or subacute yellow atrophy of the liver.

Acute hemolytic anemia, as evidenced in our Case 2, is an even more common manifestation of sulfanilamide toxicity in patients to whom the drug is given directly.

Long, Bliss, and Feinstone<sup>8</sup> noted the common occurrence of a mild type of anemia, and an incidence of a more severe, acute hemolytic anemia in 2.9 per cent of 307 adults and 8.9 per cent of 101 children treated. Wood<sup>22</sup> reports an incidence of acute hemolytic anemia in 2.4 per cent of 378 adults and 8.3 per cent of 144 children following the use of the drug. Numerous individual case reports of acute hemolytic anemia due to sulfanilamide have been recorded which need not be tabulated here. This complication may be explained by the acceleration of hemoglobin metabolism and disturbance in hemoglobin formation referred to above.

The mechanism of the liver damage induced by sulfanilamide cannot be explained so satisfactorily. A number of authors,<sup>8, 12-14, 16, 20, 29</sup> on grounds which are not certain, believe that it may either be due to individual idiosyncrasy or be based upon an allergic or sensitization mechanism as with arsphenamine, cinchophen, and aminopyrine. In connection with the latter suggestion, it is a curious fact that, in a number of cases,<sup>11-13, 17, 20, 21</sup> treatment was interrupted and the evidence of liver damage developed soon after resumption of the drug; in some of these cases, symptoms of milder toxicity were present with the first course of treatment. This would suggest the possibility that in these cases an allergic mechanism in a sensitized patient was responsible for the damage. Goldman, Applebaum, and Antopol<sup>23</sup> made a similar observation in respect to cases of malignant neutropenia following the use of sulfapyridine, as did Rosenthal and Vogel,<sup>24</sup> and Volini and others<sup>25</sup> noted that sensitization may follow resumption of interrupted medication with sulfathiazole. Kracke and Parker<sup>26</sup> have dis-

cussed at some length and cited evidence in favor of an allergic mechanism of certain drug reactions. This possibility, in the case of sulfanilamide, is further suggested by a very interesting case reported by Salvin<sup>27</sup> of a 22-year-old male who, after 4 doses of 10 gr. each of sulfanilamide, developed intense, generalized itching accompanied by sneezing, shortness of breath, lacrimation, swelling of the eyelids, lips, and scrotum, and urticaria-like lesions of the face, ears, inner margins of elbows and knees, and the abdomen. The sulfanilamide was discontinued, a large dose of magnesia magma was given, and 3 drops of epinephrin administered subcutaneously; this treatment was followed by disappearance of the symptoms. Patch tests with sulfanilamide, but not with other related compounds, produced a positive reaction. A repeat dose of 1 gr. of the drug brought on a similar attack.

A similar case was reported by Schonberg<sup>28</sup> of a 21-year-old woman who was given 20 gr. of sulfanilamide every six hours on the first day, and 10 gr. every six hours thereafter for a vulvar infection. On the fourth day she developed a generalized erythematous eruption composed of wheals and macules. After an interval of one month, a single dose of 5 gr. of the drug was followed by a generalized scarlatiniform erythema with intense pruritus, acute edema of the eyelids, lips, larynx, and forehead, considerable difficulty in breathing, and pain in the chest.

Davidson and Bullowa<sup>29</sup> have listed a number of such cases in the literature which they consider examples of true acquired hypersensitivity to sulfanilamide. In these cases, "a reaction, usually chills, fever and a rash, occurred during treatment after the patient had already received a substantial amount of the drug, and was reproducible later by the administration of a small amount of sulfanilamide."

The suggestion of individual drug idiosyncrasy in some cases is supported by the observation of a number of cases in which evidence of liver damage has developed after the administration of small amounts of sulfanilamide. This mechanism was evident in a recent case observed by one of us of a 34-year-old physician, who, after a single dose of 30 gr. of sulfanilamide by mouth for an acute infection of the epiglottitis, developed severe jaundice with an icteric index of 96 which cleared readily under appropriate treatment.

#### SUMMARY

Sulfanilamide (and probably also the other sulfonamides) passes through the placenta when given to the pregnant mother and is soon present in the blood and tissues of the fetus in concentrations equal to those in the mother. This would appear to expose the fetus and newborn to the hazards of the possible toxic effects of these drugs. We report a case of acute yellow atrophy of the liver associated with necroses in other organs in a newborn infant following administration to the mother of sulfanilamide which was found in the infant on the fifth day of life in a concentration of 1.5 mg. per cent. We also report a case of acute hemolytic anemia in a newborn infant probably but not certainly due to the same mechanism. The clinical and hematologic features in

both cases suggested the apparently erroneous diagnosis of erythroblastosis fetalis.

The mechanism of the anemia following sulfanilamide administration appears to be an acceleration of hemoglobin metabolism and a disturbance in hemoglobin formation, in addition to increased hemolysis. It is suggested that other toxic reactions due to sulfanilamide may be based either upon individual idiosyncrasy or upon an allergic or sensitization mechanism.

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## CYCLICAL ESTROGEN THERAPY\*

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WITH the release of diethylstilbestrol for general use, there is need for emphasizing certain principles of estrogenic therapy that were not so important when we were limited to the use of less potent and more expensive estrogens. Besides untoward side effects peculiarly related to the gastrointestinal tract, the exact nature of which is not understood, there are other conditions that may be and have been produced and that can and should be avoided. Ovulation and menstruation can be inhibited, endometrial hyperplasia can be produced, uterine bleeding of abnormal character and profuseness may be induced, and refractoriness to the benefits of estrogen therapy in general may be developed. All of these untoward effects of diethylstilbestrol therapy may be avoided by the judicious use of *cyclical* estrogen therapy. The use of estrogens in obstetrics and their administration by inunction and the intravaginal route have been omitted from this discussion.

Long term experiments in rats and mice, which have received pellets of estrogens, unesterified estrogens daily, or estrogen esters less frequently for several weeks or months, have revealed the harmful and toxic effects of uninterrupted treatment. Growth and gain in weight have been inhibited, premature epiphyseal closure has been effected, pyometra and death due to septicemia and hepatic and renal cloudy swelling and necrosis have occurred. Metaplasia, adenoma, and carcinoma of the reproductive organs have been produced (Lacassagne,<sup>1</sup> 1935; Loeb and others,<sup>2</sup> 1936; McEuen,<sup>3, 4</sup> 1936; Freudenberg and Clausen,<sup>5, 6</sup> 1937; Gardner and Allen,<sup>7</sup> 1937; Perry and Ginzton,<sup>8</sup> 1937; Zondek,<sup>9</sup> 1937; Gardner and others,<sup>10</sup> 1938; Gaarenstroom and Levie,<sup>11</sup> 1939; Kochakian,<sup>12</sup> 1940; Russell and others,<sup>13</sup> 1941; Page and others,<sup>14</sup> 1941).

Aplastic anemia has been produced in normal dogs of both sexes and in ovariectomized dogs after treatment with large doses of estrone, estradiol benzoate, and diethylstilbestrol (Tyslowitz and Dingemans,<sup>15</sup> 1941).

Lipschütz and others<sup>16</sup> (1941) have demonstrated the toxic effects on guinea pigs of prolonged treatment with estradiol monobenzoate under different timing conditions. Thus, a given quantity of estrogen administered over a period of sixteen weeks produced hyperplasia, polyps,

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fibroids, and bleeding, while many times the dose administered over a longer period of time but with frequent intervals without treatment did not produce these untoward effects. Schilling and Laqueur<sup>17</sup> (1941) have shown that continuous treatment of thyrohyperplastic rats with estrone has produced a significant increase in the weight of the pituitary while intermittent doses ten times as large but administered at ten-day intervals did not affect the pituitary to a degree that was statistically significant.

Cyclical estrogen therapy, on the other hand, has produced no such untoward effects. In this laboratory, where several thousand mice have been used for estrogen bio-assay, many of them for periods of six to twelve months, the mortality among test animals does not differ significantly from that of the rest of the animal colony. In spite of the fact that each animal receives a dose of estrone of from 0.2 to 2.0 micrograms or equivalent urinary estrogen once each week (cyclically), genital tumors and pyometra have not occurred.

The problem of dosage of estrogens may be of utmost importance from the standpoint of degree of effectiveness of the hormone on the organism. Selye<sup>18</sup> (1940) has reported an acquired resistance to estrogen overdosage without antihormone formation. His conclusions were based on experiments on rats receiving prolonged daily treatment with estradiol and diethylstilbestrol. Thus he showed by means of weight curves that "animals, which following an initial state of weight loss, had adjusted themselves to the treatment sufficiently to gain weight in spite of continued treatment, eventually lose weight again and finally die. . . ." Experiments are in progress in this laboratory which show by other criteria the development of a refractoriness to estrogen in the rhesus monkey when treatment is continued over a long period of time without interruption. The method of continuous treatment was by hormone pellet implantation in this study.

In a recent paper (Palmer and Dow,<sup>19</sup> (1941), it was shown that cyclical estrogen therapy to mice with *threshold* doses of estrone provoke the greatest possible reactivity to subsequent estrone treatment. Thus a positive correlation between past and present estrogenic response to threshold doses of estrone has been demonstrated. Decreased sensitivity to estrone appears to follow treatment with doses well below or well above threshold doses.

Bishop and McKeown<sup>20</sup> (1941) have reported that doses of estrone which by daily injection produce continuous estrus in ovariectomized mice did so for short periods only and had to be followed by gradually increasing doses in order to maintain a state of continuous vaginal cornification. Zuckerman<sup>21</sup> (1941) in his experiments on artificial menstruation has observed a definite effect of previous on subsequent responses of rhesus monkeys to estrogens. His observations on subhuman primates appear to have clinical bearing.

The undesirable effects of prolonged estrogen administration to human beings have been reported by Zondek<sup>22</sup> (1940). The normal ovarian



cycle has been inhibited with the production of amenorrhea for seventy days by the injection of 70,000 I.U. of estradiol benzoate. Zondek has produced cystic glandular hyperplasia of the endometrium, inhibited corpus luteum formation, and stimulated adenomatous (eosinophilic) hyperplasia of the anterior lobe of the pituitary. I have observed complete inhibition of menstruation for as long as two cycles in several patients taking 1 mg. of diethylstilbestrol daily for that period of time.

The ease with which cyclical bleeding can be produced in patients with primary amenorrhea along with the development of secondary sex characteristics using threshold doses of diethylstilbestrol cyclically has been reported (Palmer,<sup>23</sup> 1941). Adequate estrogen dosage has been particularly expedient in controlling abnormal uterine bleeding. The rationale for such therapy has been discussed in a previous publication (Palmer,<sup>24</sup> 1941).

Hamblen and others<sup>25</sup> (1941) advocate cyclical estrogen and progestogen therapy in young women with menometrorrhagia and have administered a total of 217 cycles of such treatment to 51 patients. Surgery and radiation procedures have been obviated in their series. Cyclical estrogen therapy has been recommended by MacBryde and others<sup>26</sup> (1941), who have treated 202 women with estrogen deficiency. Their series consisted of women with natural or artificial menopause and young women with amenorrhea and primary hypogonadism. They have found that from 0.3 to 0.5 mg. diethylstilbestrol daily for two to three weeks is an adequate monthly requirement and that the incidence of nausea is 8.6 per cent on interrupted treatment as compared with 20 per cent on continuous treatment.

The means at our disposal for determining the therapeutic dose of an estrogen are rather limited. Therapeutic dosage can be ascertained by the relief obtained from symptoms in menopausal patients, histologic changes in the endometrium, and changes in the vaginal pH and vaginal smear. Insufficient dosage is judged by incomplete relief of symptoms of the menopause, failure of significant lowering of the vaginal pH, inadequate change in the vaginal smear or inactivity in the endometrium. Overdosage, on the other hand, cannot be judged by over relief of symptoms or by changes in the vaginal pH or vaginal smear. Overdosage can, however, be detected by the production of hyperplasia of the endometrium. Wenner and Joël<sup>27</sup> (1939), Wenner<sup>28</sup> (1940), and Palmer<sup>23</sup> (1941) have determined the therapeutic dose of diethylstilbestrol to be in the neighborhood of 40 to 50 mg. per cycle, using the endometrium as the indicator of adequate but not excessive dosage. This amount of estrogen in the case of diethylstilbestrol is greatly in excess of that amount reported by practically all observers for the relief of menopausal symptoms. There is obviously a wide variation in therapeutic dosage of estrogens. When the attempt, however, is being made to produce tissue growth, such as is desired in genital in-

fantilism, and failure in the development of secondary sex characteristics in the female, it is logical to pursue a course by which the most marked effects can be produced without fear of overdosage.

Occasionally it has been observed that the vaginal mucosa, endometrium, and mammary tissue are refractory to estrogenic hormone. It is not unlikely that this refractoriness may account to some degree for the failure of development of these tissues in individuals with primary amenorrhea and genital infantilism, thus accounting for the apparently large doses of diethylstilbestrol required for their development. The

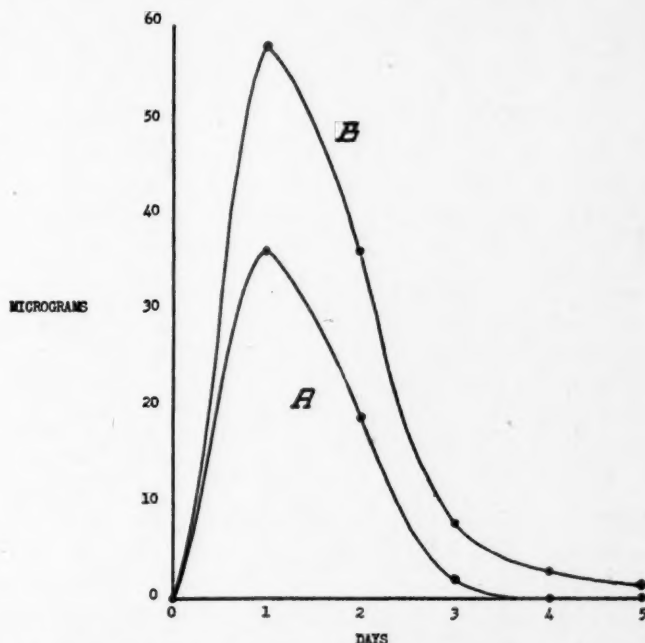


Fig. 1.—Estrogen excretion following a single intramuscular injection of diethylstilbestrol in oil. A, after 1 mg., B, after 2 mg. (Composite curves compiled from our data and that of Mazer and others, 1941; estrogen in terms of estrone equivalent.)

menopausal woman, on the other hand, has experienced a reproductive period in her life, and for her the therapeutic dose of estrogen is likely to be less, probably in the neighborhood of 0.3 to 0.5 mg. per day. This is offered in argument for the view that the therapeutic dose of diethylstilbestrol varies widely, depending upon the purpose for which the hormone is intended.

We carried out estrogen recovery experiments to compare the excretory level of estrogen of individuals without any ovarian function but who had received diethylstilbestrol, with that of the normal woman, and to determine the proper spacing of diethylstilbestrol administration. In Fig. 1 there are composite curves that show the daily estrogen

excretion following a single intramuscular injection of 1 and 2 mg. (Curves A and B, respectively), of diethylstilbestrol. It can be seen that "peak" excretion occurs during the first twenty-four hours after the intramuscular injection of a dose of diethylstilbestrol. Fig. 2 shows the theoretical type of intermittent estrogen excretion that may be expected by a patient given weekly injections of 1 mg. diethylstilbestrol. Fig. 3 shows estrogen excretion curves compositely compiled from Mazer's<sup>20</sup> data (1941), associated with daily oral administration of diethylstilbestrol. The relative constancy with which the excretory

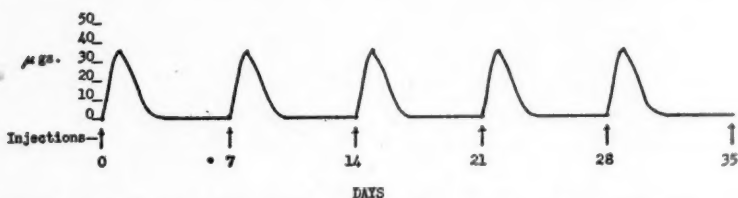


Fig. 2.—Theoretical estrogen excretion following intramuscular injections of 1 mg. diethylstilbestrol at weekly intervals. (Elaborated from Curve A, Fig. 1.)

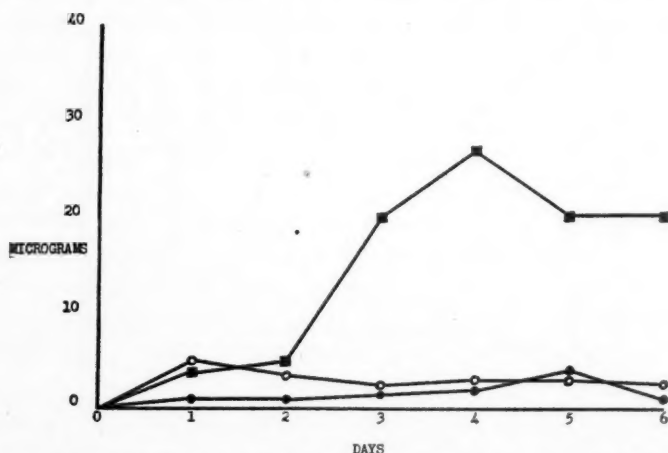


Fig. 3.—Estrogen excretion following daily oral administration of diethylstilbestrol: ●, 0.1 mg. daily; ○, 0.2 mg. daily; ■, 0.5 mg. daily. (Composite curves compiled from the data of Mazer and others, 1941; estrogen in terms of estrone equivalent.)

level of estrogen is maintained when diethylstilbestrol is administered daily by the oral route is obvious. The average daily excretion of estrogen by a normal woman has been found to be 12 micrograms (estrone equivalent) with the range of excretory values being 4 to 30 micrograms per day (Palmer,<sup>30</sup> 1937).

As far as excretory studies are concerned, 40 to 50 mg. of diethylstilbestrol per cycle, as used for the production of anatomic changes in an individual, is associated with an excretion of estrogen greatly in excess of that of the normal woman. Thus the daily administration of

from 0.2 to 0.5 mg. of diethylstilbestrol is followed by estrogen excretion that is comparable to that of the normal woman. It is on this basis that we recommend the therapeutic dose of diethylstilbestrol for the relief of menopausal symptoms to be in the neighborhood of 0.2 mg. to 0.5 mg. per day. The dose of other estrogens that may be used can be determined from Table I.

TABLE I. APPROXIMATE AMOUNTS (MICROGRAMS) OF VARIOUS ESTROGENS REQUIRED TO PRODUCE ESTRUS IN 50 PER CENT OF GROUPS OF OVARECTOMIZED MICE (EMMENS,<sup>35</sup> 1938)

ESTROGEN (1)	BY INJECTION (2)	BY MOUTH (3)
Ethinyl estradiol	0.020	1.2
$\alpha$ -Estradiol	0.025	1.1
Diethylstilbestrol	0.100	0.4
Estrone	0.100	1.0
Estriol	1.100	3.0

It is apparent from data in Figs. 1, 2, and 3 that if a continuous excretory level of estrogen is to be maintained dosage of the hormone must be administered at least daily. It is also apparent, since daily *injections* of any drug are objectionable when another route is just as efficacious, that oral administration (hormone feeding), or possibly inunction, is the most practical means of effectively maintaining an excretory level of estrogen. Thus it would seem that for those individuals who are able to tolerate orally active estrogens, daily or divided daily doses should be most efficient and practical. Cyclical estrogen therapy for the human being, then, should consist of three weeks of daily hormone feeding followed by a week or more without treatment. If the seven to ten days without treatment falls at the time of expected menstruation in those individuals who have a uterus and who are still menstruating, the production of prolonged or irregular bleeding or amenorrhea can be obviated.

Although the estrogen-withdrawal-bleeding interval has been found to be quite constant in patients with primary amenorrhea and natural menopause, this is not the case in women with varying degrees of ovarian function exhibiting normal or abnormal menstrual cycles. The mechanism responsible for the variation in the estrogen-withdrawal-bleeding interval has been described elsewhere as being a theoretically fluctuating uterine threshold and will not be gone into here (Palmer,<sup>23, 24</sup> 1941). At any rate, it has been found in our series of patients being treated for the menopause by hormone feeding that the beginning of a cycle of estrogen therapy should be the second or third day of a phase of bleeding and that the daily dose given be large enough to stop effectively that phase of bleeding within two or three days. If estrogen withdrawal bleeding occurs at all (when the estrogen used is diethylstilbestrol), it will do so at most seven to eight days after cessation of treatment. Our

estrogen recovery data have revealed that excretion of estrogen ceases, regardless of the dosage, in ovarian inactive individuals in that period of time, and by this criterion we may assume that elimination from the body is complete. No estrogen whatsoever was found in their urine seven days after each of the two patients had received 5 mg. a day for a period of seven days. On the basis of estrogen recovery data, it would seem that the shortest interval between cycles of estrogen therapy should be no less than five days. The interval may be as long as desirable, occasionally, to check the patient's need for further treatment. If, however, the withdrawal bleeding that occurs is alarming as to its profuseness or prolongation, further cyclical therapy should be instituted. When a series of cycles of estrogen therapy has been planned, the successive cycles should be started the second or third day of a phase of withdrawal bleeding just as the first cycle of therapy should be instituted on the second or third day of a phase of spontaneous bleeding.

It has frequently been found that the daily dose of estrogen required in cyclical therapy for the menopause is small enough so that the withdrawal intervals are not associated with bleeding or that in individuals in whom withdrawal bleeding has been induced the dose can be lowered and still be effective, so that withdrawal bleeding does not recur. On the other hand, it has also been found that some individuals seem to require a daily dose, for the relief of symptoms, that is always followed by bleeding during the withdrawal intervals. Irradiated patients are the least likely to have withdrawal bleeding even with sizable doses. Hysterectomized women, if hysterectomy has been adequate, of course do not bleed, and it is in these cases where the need for cyclical estrogen therapy may justifiably be questioned. Because of the experimental observations reported above in which uninterrupted treatment has been shown to produce harmful effects and because even the most experienced of us are still in the early phases of investigation of potent estrogen therapy, it would seem advisable that cyclical therapy should be observed in all cases, even though uterine bleeding is not a factor with which we need to contend.

#### THE USE OF ESTROGEN ESTERS

The protracted effect of estrogen esters has been established in the laboratory by many workers (Miescher and others,<sup>31, 32</sup> 1938), and the protracted effect of them in human beings has been observed by most clinicians who have used and compared the effects of esterified and unesterified estrogens. Weight for weight, the dipropionic acid ester of  $\alpha$ -estradiol has been found to be the most protracted in its effect in experimental animals and it seems also to be most enduring in its effect clinically. Heavier estrogen esters by virtue of increased length of the nonestrogenic hydrocarbon radicals have been used in the laboratory



and found to have an even greater protracted effect, the protraction varying directly with the length of the side chains. The dipropionic ester of  $\alpha$ -estradiol, however, is the largest molecule available commercially for clinical use at present.

Accurate estrogen-withdrawal-bleeding data for estrogen esters in human beings are not available at present. It is possible to state, however, from observations on primates (Engle and Crafts,<sup>33</sup> 1938; Zucker-  
man,<sup>21</sup> 1941) that contrary to the fact that the estrogen-withdrawal-bleeding interval does not vary markedly with the dose of unesterified estrogen used, the interval does vary directly with the dose of estrogen ester used.

The use of estrogen esters is to be preferred in individuals who cannot tolerate hormone feeding. Small doses from 0.1 to 1.0 mg. at intervals probably not less than seven days can be administered, usually without the advent of endometrial stimulation and bleeding. If larger doses are required for the relief of symptoms, intervals of two weeks or longer after a series of three or six weekly injections probably should be observed for the occurrence of withdrawal bleeding in the rhesus monkey. The larger the dose used the longer the withdrawal interval should be. The restarting of a cycle of therapy with an estrogen ester may be made with the onset of a menstrual period or a phase of withdrawal bleeding.

Cyclical therapy by hormone feeding has, in our hands, produced the best immediate results and has been the most economical and practical. Some patients who have been followed have required no more than one cycle of treatment, with the occasional repetition of a second cycle of treatment a few months later. If a second cycle seems indicated immediately, then plans are made to follow a cyclical regime for six months before stopping treatment. This plan may be followed by the failure of recurrence of menopausal symptoms when the six months' regime has ended. However, the problem of how it will all end for those few patients for whom cyclical estrogen therapy seems to be required month after month remains unsolved for the present.

There is some experimental data to support the view that estrogen esters may yet prove the preferable means by which the treatment of the menopausal woman can be carried out most successfully. Markee<sup>34</sup> (1940) has observed that gradually decreasing doses of estrogen make for the prevention of withdrawal bleeding. This is the effect in a general way of estrogen esters as compared with unesterified estrogens (Engle and Crafts,<sup>33</sup> 1938). Where withdrawal bleeding may be a desirable result, as in primary amenorrhea, such bleeding is most efficiently produced by large doses of unesterified estrogens being suddenly withdrawn. The sudden fall in estrogen level produced in this manner is usually followed by uterine bleeding. This effect is not so easily produced with hormone esters having a protracted effect or by the

use of pellets of estrogen. In an experiment on a rhesus monkey where diethylstilbestrol pellets were implanted subcutaneously, complete absorption of the pellets took place and cystic glandular hyperplasia of the endometrium was produced but bleeding did not occur even after a sufficient interval was observed.

#### CLASSIFICATION OF ESTROGENS

Estrogens may be classified in at least three ways: First, according to their relative potencies as determined by a standard laboratory procedure; second, according to their relative potencies by oral vs. parenteral administration; and third, according to their duration of action. Peculiarities in chemical structure, solubility, absorption, fate and excretion of estrogens prohibit any sort of correlation between these three classifications.

Emmens<sup>35</sup> (1938) has determined the data necessary for classification of estrogens according to the first two points. Table I lists the estrogens with which we may be concerned in the order of their potency as determined by a standard procedure. Column 2, Table I, lists the least amount of crystalline hormone in micrograms by injection necessary to produce estrus in 50 per cent of a group of ovariectomized mice. Column 3, Table I, lists the least amount of crystalline hormone in micrograms which by oral administration is necessary to produce estrus in 50 per cent of a group of ovariectomized mice.

The third point in the classification of estrogens is simply one of grouping them either as simple estrogens or estrogen esters and can be appreciated only when administration of them is by injection. All of the estrogens themselves are relatively short lived and have a transient effect while their esters are long lived and protracted in action.

#### SUMMARY AND CONCLUSIONS

The harmful effects of continuous as opposed to cyclical estrogen treatment in experimental animals and human beings have been reviewed and discussed. The release of diethylstilbestrol for general use makes it necessary to observe certain principles of treatment that were relatively unimportant before the advent of inexpensive and highly potent estrogens.

The recommended therapeutic dose of diethylstilbestrol for cyclical therapy in menopausal women varies between 0.1 and 0.5 mg. daily by mouth for twenty-one days, followed by a five- to ten-day interval without therapy. The estrogen withdrawal interval should fall at the time of expected menstruation, and cycles of therapy should be started twenty-four to forty-eight hours after the onset of a new phase of uterine bleeding if it occurs.

The recommended therapeutic dose of diethylstilbestrol for cyclical therapy in young women with hypoovarian amenorrhea or primary

hypogonadism is 1 mg. daily for seven days followed by 5 mg. daily for seven days (total dose 42 mg. in fourteen days). The estrogen withdrawal interval should be fourteen days, so that subsequent cycles of therapy may be started at twenty-eight-day intervals.

Cyclical, as opposed to continuous, estrogen therapy is strongly recommended in all hypoovarian conditions, even though the absence of the uterus precludes the occurrence of bleeding as a troublesome factor.

At least daily, as opposed to less frequent, administration of diethylstilbestrol or other unesterified estrogens during a cycle of therapy is recommended for the purpose of maintaining an excretory and probably a circulating estrogen level.

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## GLOMERULAR FILTRATION AND RENAL BLOOD FLOW IN "NORMAL" PATIENTS FOLLOWING TOXEMIAS OF PREGNANCY

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### INTRODUCTION

THE frequency with which the "toxemias of pregnancy" tend to recur<sup>1, 2</sup> together with the high incidence of hypertensive disease and the vascular and renal pathology<sup>3-5</sup> which obtain in posttoxemic women has formed the basis for many of the etiologic concepts of the disease and has greatly influenced the methods of therapy in the acute phases as well as in the care of the patient post partum.<sup>6</sup>

It is not infrequent, however, to find patients who have had one of the clinical types of the disease but who fail to demonstrate any residual pathology by clinical and laboratory methods and who go through a subsequent pregnancy in a normal manner. The presence of such patients has played a large part in leading many students of the disease to believe that "toxemia of pregnancy" is not a clinical entity but is in reality a syndrome associated with several basic diseases and becoming manifest during a pregnancy.<sup>7</sup> It is believed that the amount of renal and vascular damage found in prolonged follow-up studies<sup>8-10</sup> is proportional to the length and severity of the acute ante-partum stage.

We were unable to demonstrate an increased incidence of hypertension in any age group among women who had had term pregnancies when compared with patients who had never been pregnant.<sup>11</sup> These results were interpreted to mean that the "toxemias of pregnancy" leave no residual hypertension-producing lesion, but that the disease probably occurs in only those patients who have a "hypertensive type" of vascular system.

In routine examination of apparently normal patients by the diodrast clearance, it has been noted in some cases that the renal blood flow is definitely depressed,<sup>12, 13</sup> although a depression of this function is usually associated with hypertension. A definite depression of the renal blood flow has been demonstrated immediately post partum in the "toxemic" patient<sup>13, 14</sup> although it may be normal prior to delivery.<sup>13-15</sup>

Such observations suggest that clinically normal patients may have the same inherent vascular pathology as subjects with outspoken hyper-



tensive disease. It seems likely that one might encounter a greater incidence of nonhypertensive vascular disease as well as of hypertensive vascular disease among posttoxemic women than in the population at large.

The following experiments are designed to determine the incidence of depressed renal blood flow in "posttoxemic" women who are normal to other clinical and laboratory tests.

#### MATERIALS AND METHODS

Six patients who were at term and known to have had a toxemic pregnancy from one to five years previously were studied before the onset of labor and again seven to ten days post partum. Two of the patients had had one normal pregnancy since the one associated with the toxemia, two had had normal pregnancies prior to the abnormal one, and two had had only the previous pregnancy which was associated with hypertension and albuminuria.

Nine patients who had had a pregnancy toxemia from six months to twelve years previously were not pregnant at the time of the study.

All patients were known to have had a hypertension and albuminuria associated with a pregnancy and all but one had had several blood pressure recordings and urine examinations since that time. No patient was included on whom the record of the antenatal course and delivery was not available and on whom the follow-up had shown an elevation of blood pressure of 140 and/or 90 mm. Hg. or more, albuminuria, or evidence of eye ground changes.

At the time these renal function tests were done, each patient was thoroughly studied clinically. Blood pressure readings below 140 systolic and 90 diastolic were considered normal. The urine was found negative to Esbach's solution and microscopic examination of centrifuged sediment showed no abnormal constituents. The eye grounds were carefully examined and found normal. No cardiac enlargement or peripheral vascular thickening was noted.

The technique used for the renal function studies was the same as that described previously,<sup>12</sup> except that the bladder was routinely washed with 30 c.c. of saline which was expelled by 100 c.c. injections of air and that all diodrast determinations were made by Alpert's method.<sup>16</sup>

#### RESULTS

*Patients in Normal Pregnancy Following Toxemic Gestation.*—Five of the 6 patients of this group were studied antepartum, and a summary of the clinical and laboratory findings are given in Table I.

In one patient no satisfactory clearances could be obtained because of low urine flows. The inulin clearance values in the remaining 4 showed normal values for 2 and definite depression of this clearance in the other 2. The mean was found to be depressed to 84 c.c. per minute as compared with 116 c.c. per minute for the normal.<sup>13</sup> The diodrast clearance was definitely depressed in one patient but the remaining 3 of this group showed nearly normal values. The mean for the group (499 c.c. per minute) was definitely below the normal mean of 636 c.c. per minute. As is to be expected, the renal blood flow is likewise minimally depressed and the filtration fraction is found to be approx-



TABLE I  
SUMMARY OF CLINICAL DATA AND CLEARANCE VALUES OF SIX PATIENTS WITH PREVIOUS TOXEMIA OF PREGNANCY DURING A NORMAL PREGNANCY\*

CASE	AGE	PARTY	WEEKS A.P. DAYS P.P.	BLOOD PRES- SURE MM. HG.	ALB.	C.V.	YEARS SINCE TOX- EMIA	INULIN CLEARANCE C.C./MIN.	DIODRAST CLEARANCE C.C./MIN.	RENAL BLOOD FLOW C.C./MIN.	UREA CLEARANCE C.C./MIN.	URIC ACID CLEAR- ANCE C.C./MIN.	FILTRATION FRACTION	REMARKS
1A	28	2-0-2	n.d.	120/80	0	44	5	128 100	480 540 530	840 960 940	119 117 103	47 37 34	0.26 0.19	1st Preg. 1936, M.P.E. 2nd Preg. 1938, normal
2A	38	4-2-1	40	120/80 110/70	0 0	34 32	5	61 58 56 60 60 61	530 650 455 392 393	800 990 680 590 580	52 57 55 57	30	0.11 0.09 0.13 0.15 0.15	1st Preg. 1936, S.P.E. 2nd Preg. 1939, normal
3A	33	3-0-0	40	120/70 130/85	0 0	38 43	4	102 121 125 121	530 412 373	860 720 680	90 73 71	35 43 35 32	0.20 0.29 0.31	1st Preg. 1935, normal 2nd Preg. 1936, normal 3rd Preg. 1937, S.P.E.
4A	25	2-0-1	38	120/70 110/60	0 0	36 38	2	77 64 71 44 47	330 282 345 216 275 305	515 440 545 345 450 490	50 58 58	11 15 12 12 11 12	0.23 0.23 0.21 0.2 0.17	1st Preg. 1937, normal 2nd Preg. 1939, S.P.E.
5A	20	1-0-1	40	138/85 130/70	0 0	28 43	1	151 135 143 129 139	440 315 640 690	850 850 1000 1050	66 76 66 55 52		0.29 0.31 0.20 0.20	1st Preg. 1940, S.P.E.
6A	30	3-1-0	40	130/70	0	35	1	84.1 97.9	499.6 394.3	750.0 690.4	59.0 77.8	17.6 29.2	0.1854 0.2245	1st Preg. 1940, M.P.E.
Ante-partum mean Post-partum mean														

\*In this and the following table, Ecl., denotes eclampsia; M.P.E., mild pre-eclampsia; and S.P.E., severe pre-eclampsia; n.d., not done.

imately normal (0.18). The urea clearance seems to be definitely depressed in each instance and the mean is found to be 59.0 c.c. per minute. The uric acid clearance is found to be normal in two instances and definitely depressed in two; the mean is minimally depressed (17.6 c.c. per min.).

Post-partum clearances were run on 5 of the patients and satisfactory clearances obtained. In 2 instances the clearance of inulin was more than moderately decreased and in the remaining 3 the values were normal. The mean was minimally depressed (97.9 c.c. per minute) but tended to return toward normal as compared with the ante-partum value. The diodrast clearance gave normal values in only one instance and in one patient was extremely depressed. The mean tended to deviate from normal following delivery and represents a considerable reduction in this clearance (394 c.c. per minute). The renal blood flow parallels the diodrast depression and is likewise noticeably decreased (690 c.c. per minute). The filtration fraction (0.22) remains about normal although slightly higher than the ante-partum value. The urea clearance rises to 77 c.c. per minute. The uric acid values were obtained on only two patients.

*Posttoxicemic Nonpregnant Patients.*—The values for both the clinical and the laboratory studies are given in Table II.

The inulin clearance seems to be depressed in direct proportion to the time elapsed since the toxemic pregnancy and no normal values are obtained for those who are more than one year post partum. The mean for the group (94 c.c. per minute) is reduced. The diodrast clearance is definitely normal in only 3 patients, only one of whom was more than one year post partum. In two patients the values are severely reduced. The mean (468 c.c. per minute) is definitely low and the blood flow in the kidneys (780 c.c. per minute) parallels this low value. The filtration fraction remains normal (0.20) and the urea clearance is minimally depressed (78 c.c. per minute) but not remarkably so. The uric acid clearance is normal (30 c.c. per minute).

#### DISCUSSION

The patients in this series were examined clinically and by the usual laboratory renal function studies and were considered entirely normal. One group had sustained an additional test, that of the pregnancy, and failed to show evidence of renal or vascular abnormality. In this group both the renal blood flow and the glomerular filtration rate were reduced, similar to values seen previously in pregnant women who were known to be hypertensive before pregnancy and who showed hypertension and albuminuria during the tested pregnancy.<sup>13</sup> It seems reasonable to suppose that all patients who have had toxemia of pregnancy have the same vascular lesion regardless of the blood pressure level.

Some factor associated with pregnancy in these patients, as in those previously reported, apparently has the ability to increase the renal blood flow and to decrease glomerular filtration.

The clinical implications of these findings are of interest and deserve further investigation. If a patient having hypertension following a toxemic pregnancy is advised against a future pregnancy, it would seem

TABLE II. SUMMARY OF CLINICAL DATA AND CLEARANCE VALUES OF NINE PATIENTS WITH PREVIOUS TOXEMIA OF PREGNANCY WHO ARE NOW NORMAL

CASE	AGE	PARITY	BLOOD PRES- SURE MM. HG.	YEARS SINCE TOXEMIA TYPE OF TOX.	C.V.	INULIN CLEARANCE C.C./MIN.	DIOBRAST CLEARANCE C.C./MIN.	RENAL BLOOD FLOW C.C./MIN.	UREA CLEARANCE C.C./MIN.	URIC ACID CLEARANCE C.C./MIN.	FILTRATION FRACTION
1B	32	1-0-0	130/85	12 years S.P.E.	38	52 53	475 440	770 715	85 77	38 32	0.11 0.12
2B	45	6-4-2	120/74	9 years S.P.E.	40	73 80	650 520	1080 870	82 74	35 32	0.18 0.15
3B	40	2-0-1	130/88	6, 4 years S.P.E.	37	95 94 94	425 425 460	680 680 735	60 75 65	21 17 26	0.22 0.22 0.20
4B	26	1-0-0	120/70	3 years Ecl.	30	98 95	325 355	465 510			0.30 0.27
5B	28	1-0-0	130/75	1½ years Ecl.	36	88 102	445 445	760 760	65 65 67	27 29 25	0.19 0.22
6B	22	1-0-1	130/85	1 year S.P.E.	40	68 78 79 113* 129*	390 356 325 372* 374*	650 600 600* 620* 700*	68 76 68	25 26 28	0.17 0.22 0.25
7B	30	1-0-1	130/85	1½ years S.P.E.	40	95 84 164* 137*	400 450 760* 570*	666 750 1130* 850*	81 74 93	37 28	0.23 0.19
8B	23	1-0-1	120/70	1 year S.P.E.	40	125 136 120* 128*	630 535 790* 800* 840*	1050 892 1250* 1260* 1280*	85 105	47 53	0.20 0.25
9B	25	1-0-1	130/75	½ year S.P.E.	40	147 150	680 640	1133 1067	96 86 98	25 24	0.22 0.23
Mean						94.3	468.5	780.6	78.3	30.3	0.207

\*Clearances immediately post partum after the toxemic pregnancy. The values are not included in the mean.

reasonable that a nonhypertensive posttoxemic patient should get the same advice. It would also seem likely that the greatest factor in producing vascular changes in these patients is time, and that further investigation might show that less emphasis could be placed on the interruption of the pregnancy for the mother's future welfare and more effort be made to obtain a viable baby.

The renal physiology associated with the syndrome is of considerable interest. Repeated demonstrations have been made in hypertensive disease that the filtration fraction is increased, i.e., glomerular filtration is not reduced proportionately to the renal blood flow,<sup>17, 18</sup> but most of this work has been done on male subjects. The increase in filtration fraction has been interpreted as being caused by a constriction of the efferent arteriole of the glomerulus without concomitant constriction of the afferent vessel. Lampert<sup>19</sup> has recently devised a formula for calculating the resistance in arterioles of a fixed system with values obtained by the inulin and diodrast clearances. We have applied this formula to our data (Table III) and find that the total arteriolar resistance is minimally increased in our posttoxemic patients as compared to our normal group.<sup>13</sup>

TABLE III. CALCULATED AFFERENT AND EFFERENT ARTERIOLAR RESISTANCE BY POISEUILLE'S LAW SHOWING MINIMAL CHANGES EFFECTED BY ALTERED RENAL BLOOD FLOW AND FILTRATION AS COMPARED TO THAT PRODUCED BY ELEVATION OF SYSTEMIC BLOOD PRESSURE\*

GROUP	FILTRATION FRACTION	RENAL BLOOD FLOW	MEAN BLOOD PRESSURE	P <sub>G</sub> GLOMERULAR PRESSURE	RA AFFERENT ARTERIOLAR RESISTANCE	RE EFFERENT ARTERIOLAR RESISTANCE	R TOTAL ARTERIOLAR RESISTANCE	RA/RE
Normal pregnancy (ante partum)	0.18	950	100	57.22	32.77	20.10	44.07	1.190
Normal pregnancy (post partum)	0.22	979	100	60.74	19.67	22.35	42.02	0.880
Posttoxemic (antepartum)	0.19	750	100	57.91	29.45	25.71	55.16	1.145
Posttoxemic (post partum)	0.22	690	100	59.70	28.99	30.71	59.70	0.944
Posttoxemic (nonpregnant)	0.21	781	100	59.00	26.88	24.54	51.42	1.095
Hypothetical hypertensive, normal	0.22	1000	160	60.74	79.26	21.90	101.15	3.619

$$*P_g = P_o' + 20$$

$$RA = \frac{P_m - P_o' - 40}{HD}$$

$$RE = \frac{(1 - kF)(P_o' - P_o + 10)}{HD}$$

$$R = RA + RE$$

P<sub>o</sub>' = Osmotic pressure of unconcentrated blood in mm. Hg.

P<sub>o</sub> = Osmotic pressure of concentrated blood in glomerulus in mm. Hg.

HD = Renal blood flow.

P<sub>m</sub> = Average of systolic and diastolic brachial artery pressure.

These changes in arteriolar resistance, however, are minimal and certainly of no great significance when compared with resistances computed on a hypothetical case having normal diodrast and inulin clearance values but a moderately elevated mean pressure (Table III). The values for total resistance and afferent arteriolar resistance are markedly increased in such a case, whereas the efferent arteriolar resistance and glomerular pressure are unaltered.

If this formula can be applied in general to a dynamic system such as the vascular bed, it would seem that the fundamental physiologic basis of this disease is reduced vascular flow, specifically through the kidney. Alteration in vascular tone (spasm) ensues only after hypertension develops and merely serves to maintain the low flow.

#### SUMMARY

Renal blood flow and glomerular filtration have been determined on 6 pregnant and 10 nonpregnant women who have had a toxemia of pregnancy from one to twelve years previously and who have been considered normal by both clinical and laboratory methods since.

Reduction of the renal blood flow and glomerular filtration is noted on most patients and is generally correlated with the length of time since the toxemic pregnancy.

The presence of a pregnancy usually is associated with higher values than are noted post partum, but the findings in these patients are not unlike those in the posttoxemic hypertensives who have a recurrent toxemia.

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# THE ROUTINE USE OF BICYCLE EXERCISES FOR THE PROPHYLAXIS OF POSTOPERATIVE THROMBOPHLEBITIS

## A PRELIMINARY REPORT

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THE exact incidence of thrombophlebitis occurring as a postoperative complication is difficult to find in the various papers and monographs that appear on the subject, but Thorek<sup>1</sup> suggests it to be around 1 per cent. He states, though, that in Kümmell's clinic, at Göttingen, some thrombophlebitis was seen in more than 4 per cent of their laparotomies. He further relates that clinics of other men report figures variously from 1 to 5 per cent. Barker and his associates<sup>2</sup> recently report a study of 172,888 operative cases of which 1,665 developed thrombosis with or without embolism or embolism with or without other evidence of thrombosis. Crafoord,<sup>3</sup> in 1,054 patients subjected to operation for gynecological disorders, records an incidence of 4 per cent.

### ETIOLOGY

Any consideration of the possibility of prophylaxis for such a complication should be preceded by a knowledge of the factors which predispose to the condition. We find in a review of the available literature a wealth of information rather carefully worked out on this point.

Barker and others<sup>2</sup> in an analysis of their 1,665 consecutive cases of postoperative venous thrombosis and embolism, found that thrombophlebitis had a greater incidence in women than in men with a ratio of 3:2. The complication was rare before the age of 20 and more than 50 per cent of the cases in men were found in patients between the ages of 50 and 69 years; more than 60 per cent of the cases in women were found in patients between the ages of 40 and 59 years. It is thus seen that this complication develops in women in earlier age groups than in men.

This group studied various disorders of their patients with reference to possible predispositions for this complication and, as a result, believe that patients with the following conditions show a definite, though not marked, tendency to develop thrombophlebitis: (1) Obese patients; (2) patients with blood disease, such as, secondary and hypochromic anemias, polycythemia vera, leucemia, primary anemia, hemolytic icterus, and thrombocytopenic purpura; (3) patients with diseases of the peripheral veins, such as, varicosities or previous thrombophlebitis either recent or

old; (4) patients with cardiac disease, e.g., chronic valvulitis, hypertensive heart disease, coronary heart disease, and auricular fibrillation; (5) severe infections either as an indication for the operation or as a postoperative complication; and (6) carcinoma.

It is interesting to note that while the above may be present singly or in various combinations in some patients, there were about one-third of their patients who developed this complication and showed no evidence of any of these predisposing factors.

The fact that patients exhibiting marked varicosities of the legs are prone to develop postoperative thrombosis in these is well recognized, and hence any factor which would predispose to the development of the former might, in a way, be effective in aiding the production of the latter.

Boyd<sup>3</sup> lists four exciting factors in the production of these varicosities, i.e., (1) central obstruction to the venous return as in mitral stenosis, emphysema, cirrhosis; (2) pressure of a tumor, gravid uterus, or loaded rectum; (3) prolonged standing; and (4) straining and violent muscular efforts.

For an excellent consideration of the entire subject of thrombophlebitis with an adequate nucleus for a bibliography the reader is referred to the article by Homans on thrombosis found in Mason's text.<sup>4</sup> This investigation of the problem considers three local anatomic causes and as many general contributing causes. The first of these include: (1) The veins must be of good size; (2) the vein must have entering branches or large valves or turns or pockets which would present opportunities for eddies and confused currents; and (3) the vein usually is so situated that any of a variety of conditions can slow the current, even for considerable periods. It is readily seen how the upper femoral and iliac veins as well as the venous plexuses of the pelvis and varicosities of the legs conform to the above-mentioned conditions.

The essential points of this entire problem seem, to the author, to be summed up in Homan's discussion of the following which he calls general contributing factors. The first of these are disorders which tend to alter the vascular endothelium, the second are disorders in which the character of the blood is altered and the third are disorders causing sluggish circulation either over the whole body or part of it.

The disorders which tend to alter the vascular endothelium are found in the form of inflammations and degenerations as seen in various septic states, influenza, typhoid fever, and the like, but these are the least important practically since proof of alteration of the endothelium is lacking.

Many factors may influence the character of the blood and not the least among these are states of dehydration brought on by diarrhea, vomiting, hemorrhage, or sweating. All of these are readily recognized as being closely associated both preoperatively and postoperatively in

surgical patients. Other states influence the character of the blood, such as the toxemias, either chemical or other, nephritis, diabetes, the puerperal state, trauma of accidents and surgical procedures.

It is the third group of disorders which cause sluggish circulation that particularly concern this paper. In this class are found the immobility that so frequently follows operations or prolonged illnesses, increased intra-abdominal pressure caused by reclining or sitting up in bed, vomiting, coughing, distention, and tight abdominal binders as well as the congestion of pelvic veins as in pregnancy.

Smith and Allen,<sup>5</sup> by their studies on the rate of venous flow, noted the time required for the blood to flow from the foot to the carotid sinus in both normal individuals and in patients convalescing from operations. They concluded that there was a definite decrease in foot-to-carotid circulation time within a few hours postoperatively. Two days afterward the time was greater than preoperatively. Beginning with the fifth day postoperative, the average time increased gradually to a value which at the tenth day was approximately 50 per cent greater than the preoperative average. It was their opinion that slowed venous circulation is not the sole cause of postoperative thrombosis, but it is a very important one.

#### PROPHYLACTIC PROCEDURES

In the prevention of thrombosis and embolism, Homans attacks the problem from three different approaches. The first of these are measures to keep the fluid level normal and here the proper administration of fluids by the subcutaneous and/or intravenous routes is to be remembered. The control of vomiting, diarrhea, and hemorrhage are all items to be considered, not just for their immediate effects but for the possibility of their causing a complication at some future date as well. An important source of fluid loss, which is so frequently overlooked in our overzealous endeavor to prevent chilling of the patient postoperatively, is the sweating a patient is subjected to by the use of heavy woolen blankets on the operative day and even thereafter. It should be remembered that the temperature of the room would be better controlled and the avoidance of drafts more important than wrapping the operated patient in many blankets.

In an effort to control a rise in the intra-abdominal pressure after the operation, Homans states that one should avoid peritoneal trauma and contamination during the operation, and overloading the stomach with fluids afterward in attempting to adjust the fluid balance. The judicious use of the rectal tube early, and enemas later, will do much to relieve the accumulation of gas in the intestinal tract. Heavy dressings, and tight abdominal binders in particular, are to be avoided. The efficacy of the abdominal binder is doubted even by many men who, through years of habit, continue to use it. A point that is not generally considered is the fact that the sitting or reclining position not only in-

creases intra-abdominal pressure, but also necessitates the blood of the legs to climb to a higher level.

#### EXERCISE IN PROPHYLAXIS

The use of exercise in the prevention of this complication is not a new idea. As early as 1913, Pool<sup>6</sup> suggested the routine employment of systematic exercises in postoperative treatment. His exercises included flexions, extensions, rotations, pronations, supinations and the like, to be carried out at a certain portion of each day under the supervision of nurses. Following their use in a considerable number of patients, he was able to conclude that the general circulation was improved, the

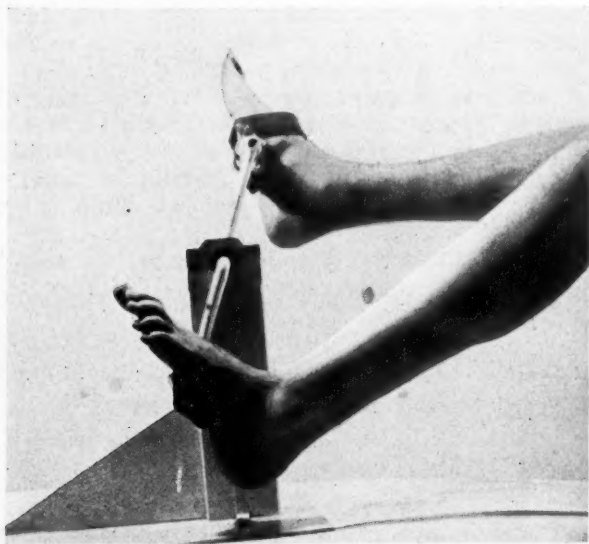


Fig. 1.

functions of the body were performed in more normal manner, the patients felt better, muscular weakness and atrophy were diminished, after getting up exertion was less fatiguing, and return to normal was more rapid.

Smith and his associates<sup>7</sup> found that rapid movement of the legs while in the supine position invariably increased the speed of the blood flow. Elevation to an angle of 30 degrees of the extremities of supine subjects invariably decreased the circulation time. This work, reported in 1941, tends to substantiate the results of Pool and other advocates of the value of exercises and elevation, in the prophylaxis of thrombosis.

Dr. A. P. Martini, formerly associated with the department of gynecology and obstetrics of St. Louis University, at the suggestion of the director of the department, Dr. W. H. Vogt, constructed an apparatus as described by Gamble.<sup>8</sup> This machine is designed with the idea of em-

playing routine exercises of the lower extremities in a manner that would require a minimum of supervision by the nursing staff and of preparation of the patient.

#### RESULTS

The regime instituted by Dr. Martini was to start the exercises on the first day after the operation. On that day, the exercises were taken twice, for five minutes each time. The patients were instructed, by the nurse in attendance, as to how to fit themselves to the apparatus, and shown about the desired speed of motion. On subsequent days, the exercises were increased to ten minutes twice each day and were continued until the patient was out of bed. Usually no care was needed for the patients during the time of these subsequent exercises and thus the nurses were free to attend to other duties.

To offset the lack of exercises on the day of operation, they had the foot of the bed elevated for the first twenty-four hours, either in the Trendelenburg position, or by simple elevation of the lower portion of the springs of the bed. This aids in speeding the venous return flow from the legs as shown by Smith and his co-workers above.

The procedure is a very simple one and is readily adaptable to routine orders on cases such as are encountered on gynecologic wards. The patients themselves are very fond of the exercises. While many of them find it somewhat difficult at first, the greater majority of the patients become very cognizant of the feeling of well-being it gives them. Some of them have requested information regarding the possible purchase of these machines for continued use at home.

The first machine is a homemade outfit, consisting of a base of wood planking. To this is attached a simple upright, likewise of wood, to the top of which are attached the bicycle pedals. When this machine was in operation for only a few weeks, we were fortunate enough to have a patient using it whose husband operated a bicycle rental business, and he made us another one with somewhat more mechanical ability.

Recently we have used the machine for the treatment of a subsiding case of thrombophlebitis before allowing the patient to sit up or get out of bed in an effort to gain back some of the lost tonus caused by the enforced period of rest and elevation for some twelve days.

Interest was instigated in the writing of this paper when, within a period of three days, two postoperative patients developed signs and symptoms of thrombophlebitis. These made themselves manifest on Oct. 10, 1941, and Nov. 2, 1941, respectively. It was around this period when a new supervisor had taken charge of the floor, and she was not thoroughly familiar with our routine. While making rounds we happened to mention to her that these were the first cases of thrombophlebitis that we knew of since the use of the bicycle exercises had been



started. Much to our surprise the sister in charge reported that neither of these patient had had the exercises. It seemed then that it would be worth while to investigate the actual number of patients subjected to this prophylactic regime and to determine the value of this form of treatment.

In going through the records of the patients admitted to the gynecologic service from July 1, 1940, to those discharged by Dec. 31, 1941, we found 705 admissions. Of these, 517 were operated cases; 376 being considered as major operations and 141 as minor operations. Such procedures as dilatation and curettage, cervical biopsies, excisions of Bartholin's cysts, fulguration of fistulous tracts, insertion of stem pessaries, cautery of the cervix and dilatation of the cervix were considered as minors. All laparotomies, colporrhaphies, trachelorrhaphies, radium implants, and colpotomies were considered as major procedures.

The earliest recorded use of the bicycle exercises was on Aug. 7, 1940, and since these were established, 209 patients had these exercises for varying periods of time from three to thirteen days; of these, 198 had major operations and 11 had minor procedures. During this same period of time, there were 308 patients subjected to various gynecologic operations who did not subsequently have the advantage of the bicycle exercises; of these, 178 had major operations and 130 had minor procedures. Of the total 517 operated cases, 6 gave rise to signs and symptoms necessitating the diagnosis of thrombophlebitis. These cases may be given briefly as follows:

CASE 1.—(40-7813.) A 54-year-old housewife was operated upon on Oct. 16, 1940, for a leucoplakia and kraurosis. A radical vulvectomy was done and bicycle exercises were specifically ordered not given as it was feared they might interfere with proper healing of the operative wound. On Nov. 1, 1940, the patient developed a pain in the right groin with a moderate temperature elevation followed later by edema of that lower extremity. She responded to treatment in the form of elevation and ice bags and was discharged on Nov. 12, 1940.

CASE 2.—(40-7881.) A 35-year-old housewife had a vaginal hysterectomy with an anterior and posterior colporrhaphy on Oct. 19, 1940, for procidentia with cystocele and rectocele. The patient ran a septic postoperative temperature course with peaks as high as  $104.5^{\circ}$  for seven days. She had bicycle exercises for the first six days when she developed a secondary hemorrhage which required packing the vagina, and the bicycle exercises were discontinued. On the tenth postoperative day she developed a typical picture of thrombophlebitis in the femoral veins of the left leg. Ice bags and elevation caused gradual return to normal in twelve days. The patient was discharged improved on Nov. 11, 1940, and when last seen in the clinic on Feb. 3, 1941, she had a persistent edema of the left leg.

CASE 3.—(41-5297.) A 46-year-old housewife had a large ovarian cyst arising from the left side removed on July 28, 1941. She was on

the private floor and received no bicycle exercises. She developed phlebitis on her seventh day which responded slowly to routine treatment, and she was discharged on Aug. 17, 1941.

CASE 4.—(41-6263.) A 44-year-old housewife had a cervical biopsy on Aug. 9, 1941, for vaginal bleeding which had its onset twenty days prior. Because of the minor nature of her operation, no exercises were given despite the fact she had marked varicosities of both legs. She developed signs and symptoms of phlebitis in the left leg on Aug. 12, 1941, but with no elevation of temperature, and these subsided with rest and ice bags so that she was discharged on Aug. 19, 1941.

CASE 5.—(41-5012.) A 30-year-old housewife had a uterine suspension on Oct. 18, 1941, for a movable third degree retroversion of the uterus. Due to an oversight of the nursing staff she did not receive exercises and on her twelfth day postoperative day developed full blown thrombophlebitis in the left leg. This responded to treatment, and the patient was discharged on Nov. 20, 1941. In this case, after twelve days, when the pain, temperature, and swelling had disappeared, the patient was given exercises to regain some of the lost muscular tonus before allowing her on her feet.

CASE 6.—(41-8541.) A 39-year-old housewife had a complete hysterectomy with bilateral salpingo-oophorectomy on Oct. 27, 1941. She did not get exercises either, due to an oversight, and on Nov. 2, 1941, her sixth postoperative day, she developed pain in the right groin with swelling of the lower leg but with no temperature change. Ice and elevation were sufficient to clear these symptoms in six days. The patient was discharged improved on Nov. 10, 1941.

#### DISCUSSION

Of these 209 patients who had bicycle exercises there were none who developed thrombophlebitis after a sufficient course of treatment. One had the exercises for six days and developed phlebitis on her tenth day. This patient had a postoperative infection as evidenced by her postoperative temperature course and the secondary hemorrhage which developed on the sixth postoperative day. We hesitate to claim that if the exercises were continued the phlebitis would not have developed since the infection was probably sufficient to produce local inflammatory processes in the veins to cause the thrombosis. It might be, too, that some readers would want to criticize the employment of the bicycle in a patient with known inflammatory processes at work as in this case, because one of the cardinal rules in the treatment of inflammation is to keep the part at rest. While this is true, and while inflammation is to be considered a factor in the production of thrombophlebitis, we employed the exercises in an effort to do away with other factors which tend to allow thrombosis to occur, namely, stasis within the vessels.

Of 308 patients, in the same period of time, subjected to operation without the advantage of bicycle exercises, five developed thrombophlebitis, an incidence of 1.6 per cent.

We realize this series is much too small to draw far-reaching conclusions, but these data are presented as a preliminary report and we are encouraged, so far, by our results.

#### SUMMARY

A presentation of the subject of postoperative thrombophlebitis is briefly given by a review of the literature on incidence, etiology, and prophylaxis. One method of prophylaxis, i.e., bicycle exercises, is proposed as advocated by Gamble, and its use in 209 cases with an incidence of thrombophlebitis of 0.5 per cent is presented. We feel that the employment of this regimen is entirely satisfactory and is simple to carry out without unduly burdening the nursing staff of any modern hospital.

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### THE IDENTIFICATION OF FETAL SQUAMAS AND THE DIAGNOSIS OF RUPTURED MEMBRANES BY VAGINAL SMEAR\*

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A SURVEY of methods proposed for detecting ruptured membranes shows that they fall into two general groups. The first, based on the demonstration of various morphologic components of liquor amnii, was originally advanced by Philipp.<sup>1</sup> His criteria were the presence in the vagina of lanugo hair, pathognomonic but found only occasionally in the present study, or of crystalline oxalates and urates which are obviously nonspecific. Numers<sup>2</sup> later modified the method, basing his diagnosis on the identification of fat droplets which also lack the specificity desirable in a diagnostic test. The available literature does not mention the use of fetal squamous (epidermic scales) for this purpose.

\*Presented in preliminary form at a meeting of the Section of Obstetrics and Gynecology, New York Academy of Medicine, December 23, 1941.

The second method depends on a shift in hydrogen-ion concentration of the vaginal contents after alkaline amniotic fluid has swept through the normally acid vaginal canal.<sup>3-15</sup> Litmus paper was first employed by Victor Gold<sup>3</sup> to indicate this significant change in pH. Bock and Wolf,<sup>4</sup> and later Bock<sup>5</sup> alone utilized the hydrogen-ion electrode for this purpose. Temesvary,<sup>6</sup> Berlind,<sup>7</sup> King,<sup>8</sup> Sannicandro,<sup>9</sup> Marchese,<sup>10</sup> and Mezzana<sup>11</sup> used bromthymol blue. Ahumada<sup>12</sup> found a chemical indicator, the exact nature of which he failed to specify, more accurate than Philipp's original morphologic method. Kushner<sup>13</sup> and Abe<sup>14</sup> compared the efficacy of bromthymol blue and nitrazine reagent, both finding the latter indicator more satisfactory. Baptisti<sup>15</sup> worked only with nitrazine reagent.

Although these investigators reported good statistical results, they recognized certain limitations inherent in the pH method. There is an indeterminate range of pH values from about 6.0 to 6.5.<sup>4, 5, 14</sup> The presence of blood,<sup>8, 12</sup> excessive vaginal<sup>14</sup> or cervical secretion,<sup>12, 14</sup> alkaline urine<sup>7, 14</sup> or antiseptic solution<sup>8</sup> in the vagina may produce a positive test with intact membranes. And conversely if the flow of liquor amnii is slight or has ceased for a time, vaginal acidity may primarily dominate or secondarily reassert itself, producing a negative test with ruptured membranes.<sup>8, 9, 11, 13</sup>

In the early part of this study comparison of the results obtained by simultaneous use of nitrazine reagent and the morphologic method to be described substantiated these limitations of the pH method.

#### THE IDENTIFICATION OF FETAL EPITHELIAL SQUAMAS

The identity of fetal squamas was established by demonstrating their presence in uncontaminated specimens of liquor amnii and vernix caseosa, and in vaginal smears from gravidas with ruptured membranes, and by observing their absence in vaginal smears from gravidas with intact membranes.

*Technique.*—To avoid contamination by epitheliums from the birth canal, specimens of liquor amnii were aspirated from intact amniotic sacs at cesarean section. After dilution with an equivalent amount of distilled water to minimize crystallization, the fluid was placed on glass slides and allowed to dry before fixation in alcohol-ether solution.

Vernix caseosa of infants delivered from the same intact amniotic sacs was spread on slides and allowed to dry. Thorough drying of vernix is necessary to prevent its dissolution when placed in the fixing solution.

Samples of vaginal fluid were obtained with a sterile glass pipette and rubber suction bulb in the manner described by Papanicolaou.<sup>16</sup> It is important in this work, as will be shown later, to draw the perineum well down and to secure the specimen entirely from within the hymenal ring. If the duration of membrane rupture is long or the case important, the pipette is rinsed in a test tube containing a few cubic centimeters of normal saline solution. This provides a reservoir from which repeated smears can be made if the original ones fail to yield positive results.

The method of staining these preparations is based on Shorr's modification<sup>17</sup> of Foot's technique,<sup>18</sup> which is in turn a modification of Masson's trichrome stain. The principal alteration from Shorr's technique is a

prolongation of staining time in Fast Green FCF from two to twenty minutes. Recently dioxane has been substituted for the ascending alcohol series as advocated by Papanicolaou.<sup>19</sup>

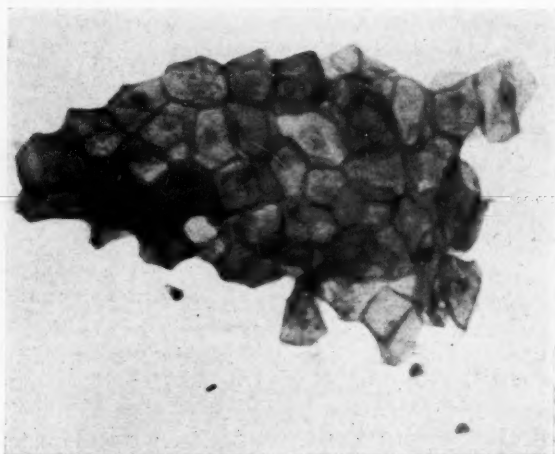


Fig. 1.—Fetal squama from a preparation of uncontaminated liquor amni. This squama represents an early stage of degeneration with slightly granular translucent cytoplasm and nuclear remnants. ( $\times 220$ .)

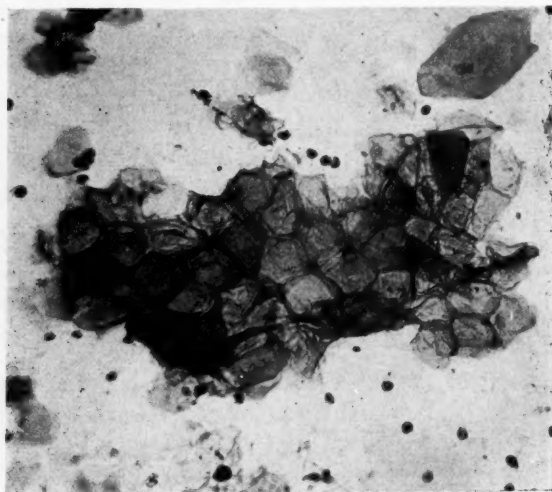


Fig. 2.—Fetal squama from a preparation of uncontaminated vernix caseosa, presenting more advanced degeneration than that in Fig. 1. The anucleate cells possess translucent crinkled cytoplasm. ( $\times 220$ .)

The smears are examined under low power, 21 to 70 microscopic magnifications being sufficient for the identification of fetal squamas. The average specimen can be obtained, prepared, and examined in less than an hour.

Vernix caseosa begins to form during the sixth lunar month of gestation.<sup>20</sup> The characteristic fetal squamas, however, described in this



study have not been consistently found in liquor amnii prior to the beginning of the ninth lunar month. From that time on, specimens of liquor amnii aspirated from intact amniotic sacs contain fetal squamas (Fig. 1), and preparations of vernix caseosa (Fig. 2) obtained from infants delivered from the same sacs indicate the origin of the squamas.

In their characteristic form (Figs. 1 and 2), fetal squamas are made up of contiguous translucent polygonal cells of which a small number may bear nuclear remnants and cytoplasmic granules. Disintegration of squamas results first in aggregates of imbricated cells, ultimately in dispersed cell units. Degenerating fetal cells finally lose both nuclear remnants and cytoplasmic granules, and the translucent cytoplasm may

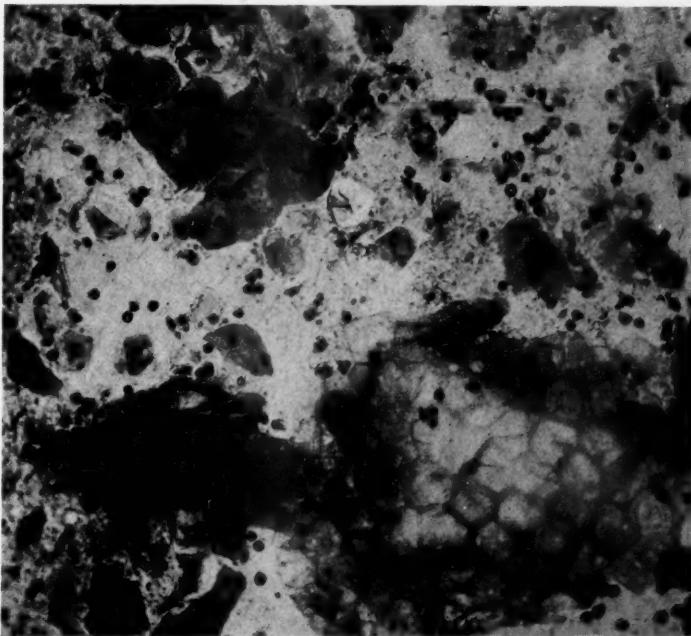


Fig. 3.—Vaginal smear from a parturient with ruptured membranes, offering morphologic comparison of a fetal squama and two groups of vaginal epithelial cells. ( $\times 220$ .)

become crinkled. Staining reactions may vary greatly from squama to squama, from cell to cell, and even within single cells. Delicate tints of emerald green, golden yellow, orange and pink are commonest. Semi-opaque cells staining darker shades of orange, red, or brown appear singly and in groups, but are not sufficiently characteristic to serve as diagnostic criteria.

With the staining technique used, vaginal epithelial cells of normal women in late pregnancy or early labor with intact membranes exhibit the typical morphologic features which have been described by Papanicolaou,<sup>16</sup> and in general they stain a uniform green or bluish

green. After the membranes rupture, intermixture of polychromatic translucent fetal cells with the more somberly stained vaginal cells produces smears with a variegated chromatic appearance. The presence of such variegation is in itself extremely suggestive of membrane rupture. The presence of some of the common antiseptic solutions (tincture of metaphen, tincture of mercesin, septisol) in the vagina does not alter the morphologic characters of the epithelial cells involved, although staining reactions may change slightly, and dilution does reduce the available number of squamas.

The morphologic differentiation of fetal squamas from sheets of cells recently desquamated from the maternal vagina, vestibule, or urethra is made on the fact that cells from these locations generally possess well-developed nuclei and granular cytoplasm which lacks the translucence of fetal cells. Fig. 3, from the vaginal smear of a parturient patient with ruptured membranes, illustrates the morphologic differences between a typical fetal squama and two groups of vaginal cells.

Degenerating squamous epitheliums, whether of fetal or maternal origin, eventually converge in their morphology. Groups of anucleate eosinophilic vaginal cells commonly occurring late in pregnancy<sup>16</sup> may closely resemble imbricated aggregates of semiopaque fetal cells staining darker shades of orange, red, or brown. Consequently such degenerated squamas are considered nonspecific. Degenerated vestibular squamas, occasionally found in smears from both pregnant and non-pregnant women, may simulate closely fetal squamas. The technique of obtaining specimens entirely from within the hymenal ring is the best available method of eliminating vestibular epitheliums as a source of error. The success of this technique suggests that vestibular cells found in the vagina have usually been artificially introduced.

The identification of a single cell type of unquestioned fetal origin has been thus far unsuccessful. This eliminates the need of minutely examining individual epithelial cells.

#### THE DIAGNOSIS OF RUPTURED FETAL MEMBRANES BY VAGINAL SMEAR

In this study the criterion evaluated for the diagnosis of ruptured membranes is the presence in vaginal smears of fetal squamas composed of contiguous translucent polygonal cells, of which a small number may bear nuclear remnants and cytoplasmic granules. Such squamas are found with marked constancy in smears from gravidas with ruptured membranes after the beginning of the ninth lunar month of gestation. There are, however, other less constant morphologic criteria which are of definite value. Lanugo hair appeared in a number of vaginal smears, and has been observed as early as the thirtieth week of gestation. Its presence may antedate that of fetal squamas. Papanicolaou<sup>21</sup> recognizes shreds of the membranes themselves as indicative of their rupture.

Such shreds may be found any time after formation of the fetal sac, and are of great value in the earlier months of gestation before fetal squamas or lanugo hair are in evidence. The recognition of membranous shreds is more difficult than that of fetal squamas, and since the present study is limited to the last two months of gestation, their incidence has not been statistically analyzed.

Three hundred and forty-four specimens of vaginal fluid from 275 patients in or beyond the thirty-second week of gestation constitute the material studied. Evaluation of the actual condition of the amniotic sac was based as much as possible on conclusive clinical criteria. These were sometimes misleading, and of necessity had to be subordinated to definite microscopic evidence. Such rejection of clinical evidence occurred for the most part in patients without clinical suggestion of membrane rupture but with irrefutably positive vaginal smears, and in cases where high leaks in the amniotic sac accompanied intact and perhaps bulging forewaters.

TABLE I. ANALYSIS OF RESULTS

CONDITION OF AMNIOTIC SAC	NO. OF PATIENTS	NO. OF EXAMINATIONS	RESULTS		ACCURACY PER CENT
			TRUE	FALSE	
Intact	150	206	204	2	99.0
Ruptured	125	138	130	8	94.2
Totals	275	344	334	10	97.1

Table I summarizes the general statistical results, indicating 97.1 per cent accuracy for the entire study. From 150 patients with intact membranes, 206 specimens of vaginal fluid were obtained. Two hundred and four yielded negative results. In 7 patients leaking fluid, believed to be liquor amnii, negative tests were later substantiated by artificial rupture of the membranes. A leak high in the amniotic sac would invalidate these tests; at the same time it would explain the two instances where artificial rupture of the membranes followed acquisition of positive vaginal smears. The latter cases occurred early in the study before the possibilities of vestibular contamination were fully appreciated, consequently they are classified as false positives.

One hundred and thirty-eight specimens were from 125 patients whose membranes were considered ruptured. In this group are 5 patients whose vaginal smears yielded positive evidence of amniotic fluid, although no clinical evidence of rupture appeared before delivery, and at the time of delivery the membranes were observed to have ruptured previously.

Table II correlates the results of these 138 tests with the duration of rupture, indicating 98.1 per cent accuracy during the first twenty-four hours of membrane rupture. Of the previous investigators who correlated their results in a similar manner, King<sup>8</sup> reported 57 per cent,

TABLE II. RESULTS CORRELATED WITH DURATION OF RUPTURED MEMBRANES

DURATION OF RUPTURE	TESTS	RESULTS		ACCURACY PER CENT
		TRUE	FALSE	
1 day	105	103	2	98.1
2 days	16	15	1	93.7
3 days	6	5	1	83.3
4 days	3	3	0	100.0
5 days	2	1	1	50.0
8 days	2	1	1	50.0
9 days	1	1	0	100.0
10 days	1	0	1	0.0
12 days	2	1	1	50.0
Totals	138	130	8	94.2

92.0  
81.8  
50.0

Sannicandro<sup>9</sup> 60 per cent and Marchese<sup>10</sup> 66 per cent accuracy for their tests, after the initial twenty-four-hour period of membrane rupture. During the same period the present method has proved 81.8 per cent correct. This figure breaks down to 92 per cent accuracy during the second, third, and fourth days of membrane rupture, and 50 per cent thereafter. Although the last figure is low, it does not lessen the value of a positive test when it is obtained.

Twenty cases where a diagnosis of the condition of the fetal membranes was requested by members of the hospital staff are presented for separate consideration as "unknowns." The initial tests on these patients resulted in 8 true positives, 11 true negatives, and one false negative which repetition of the test corrected. Eleven patients were ante-partum, 9 intra-partum. Each patient either gave a history of having ruptured her membranes or was actually leaking fluid, or both.

From these patients three diverse but sometimes combined types of vaginal smears were obtained. The presence of fetal squamas established liquor amnii as one component of the discharge; their absence indicated intact membranes. A third type of vaginal smear occurring either ante-partum or intra-partum, and with or without fetal squamas, was characterized by the presence of mucin, leucocytosis, and bacteria. This condition, clinically a watery leucorrhea or hydrorrhea gravidarum probably emanating from irritated hyperactive endocervical glands, may simulate a slight but continuous leakage of liquor amnii.

#### CLINICAL BEARING

Although the condition of the fetal membranes is of minor importance in most obstetric patients, it occasionally becomes the main factor governing their management. When clinical opinion is uncertain concerning the state of the amniotic sac, the diagnostic method presented has been of value. Ante-partum patients near term with ruptured membranes are induced with confidence in the validity of the indication for initiating labor; those suspected of ruptured membranes but proved to have intact sacs are spared premature induction of labor and

unnecessary hospitalization. Since selection of cesarean section technique is largely dependent on the condition of the membranes, proof of their integrity saves the patient an unnecessarily difficult or perhaps radical operation. Conversely, proof of membrane rupture for a period of hours indicates an extraperitoneal type of cesarean section with reduced morbidity and mortality.

#### SUMMARY

A morphologic method of diagnosing rupture of the fetal membranes is presented. It is based on a staining process which facilitates the identification of fetal squamas in vaginal smears. These squamas are composed of contiguous translucent polygonal cells of which a small number may bear nuclear remnants and cytoplasmic granules. The origin of fetal squamas was established by demonstrating their constant presence in uncontaminated vernix caseosa and liquor amnii, and in vaginal smears from gravidas with ruptured membranes during and after the thirty-second week of gestation.

This diagnostic method yields a general percentage accuracy which compares favorably with that of prior methods. Such comparison is particularly favorable in patients with prolonged rupture of the membranes. The method is unaffected by the presence in the vagina of blood, excessive vaginal or cervical secretion, urine, and some commonly used antiseptic solutions.

Clinical application of the method to the management of patients with questionably ruptured membranes is briefly discussed.

I wish to thank Dr. Samuel A. Cosgrove for his encouragement in this study, and Dr. George N. Papanicolaou for his valuable criticism of the manuscript.

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## COMPARATIVE LOCAL TISSUE REACTION AND STYPTIC ACTION OF SULFANILAMIDE\*

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TODAY, there is a widespread use of sulfanilamide locally in surgery. Almost all surgical specialties have found some use for its topical application. We have been concerned with the adaptability of sulfanilamide as a prophylaxis in pelvic surgery. Infection resulting from clean surgery is not common but does occur, and with the thought of cutting down this small group of infection we have turned to sulfanilamide. Before embarking on any such campaign in obstetric and gynecologic surgery, we have first determined its reaction to tissues encountered in our work.

### PROCEDURE

Female rabbits were used in all the experiments. After producing anesthesia with intravenous nembutal, a paste of cornstarch and barium sulfite was used to remove the fur from the abdominal wall. The skin was prepared with mercuric chloride and aseptic technique employed throughout. Intra-abdominal and musculoperitoneal sutures were of 00 plain catgut, while the skin was closed with No. 35 alloy steel wire. Dressings for the abdominal wall were made of cellophane and collodion.

### EXPERIMENTAL DATA

1. Sterile sulfanilamide powder was placed under the skin in the scant fatty tissue encountered there between muscle and the cutaneous layer. Dosage was 0.5 Gm. This procedure was carried out in nine rabbits. They were reoperated upon from two to fourteen days later. In 6 cases (66 per cent), the skin was healed, but there was a collection of from 2 to 10 c.c. (estimate) of straw-colored fluid subcutaneously, with muscle necrosis in the late cases. Two other rabbits had the same findings with complete separation of the musculoperitoneal layer, while one in the group had a wound dehiscence (Table I). Biopsies were taken routinely and in the above group fat necrosis was demonstrated.

In 30 rabbits where sulfanilamide powder was not used subcutaneously no such reaction was noted.

2. In 3 rabbits, about 1 Gm. of sulfanilamide powder was placed in the abdominal cavity. No operative steps were carried out except routine opening and closure. These cases were reoperated upon at two,

\*Presented at a joint meeting of the Baltimore, Philadelphia and Washington Obstetrical Societies, October 2, 1941.

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TABLE I. SULFANILAMIDE POWDER SUBCUTANEOUSLY

RABBIT NUMBER	DAYS LATER REOPERATED	FLUID AND NECROSIS SUB- CUTANEOUSLY	MUSCLE LAYER SEPARATION	WOUND DEHISCENCE
11	2	+		
12	2	+		
13	4		+	
16	5	+		
17	6	+		
18	7		+	
20	7	+		
28	14	+		
29	14			+

three, and four days, respectively. At that time all trace of the powder was gone, there was no free fluid, necrosis, or adhesions. There was no evidence of foreign body reaction either grossly or microscopically.

3. To investigate further the peritoneal response, we constructed artificial pouches in various parts of the abdominal and pelvic cavity. Sulfanilamide powder was placed in these pouches and sutured over. An equal number of controls were made with the same 00 plain catgut and no sulfanilamide. These rabbits were operated upon from two to seven days later and biopsies taken. Histologic study failed to reveal any difference between the peritoneum in contact with the powder and where the plain pouch had been made. Five rabbits were used in this series.

TABLE II. CONTROL INTESTINAL SERIES

RABBIT NUMBER	NO SULFANILAMIDE POWDER	MULTIPLE ADHESIONS	NO ADHESIONS	DIED FROM BLOOD LOSS AND PERITO- NEAL ADHESIONS PRESENT
50	+	+		
51	+	+		
53	+	+		
33	+	+		
31	+		+	
52	+			+
30	+			+
35	+			+

TABLE III. SULFANILAMIDE POWDER INTESTINAL SERIES

RABBIT NUMBER	SULFANILAMIDE POWDER	NO BLOOD NO ADHESIONS	MULTIPLE ADHESIONS	DIED FROM UNKNOWN CAUSE
25	+	+		
26	+	+		
28	+	+		
32	+	+		
57	+	+		
60	+	+		7 days 1 day
34	+		+	
54	+		+	
55	+		+	
57	+		+	
58	+		+	
59	+		+	

4. In continuing our work we turned to the fatty tissue as encountered around the bladder, uterine mesentery, and kidney. In 10 rabbits we made an opening in the fat and introduced 0.5 Gm. of sulfanilamide powder. The pouches in the fat were closed over. An equal number

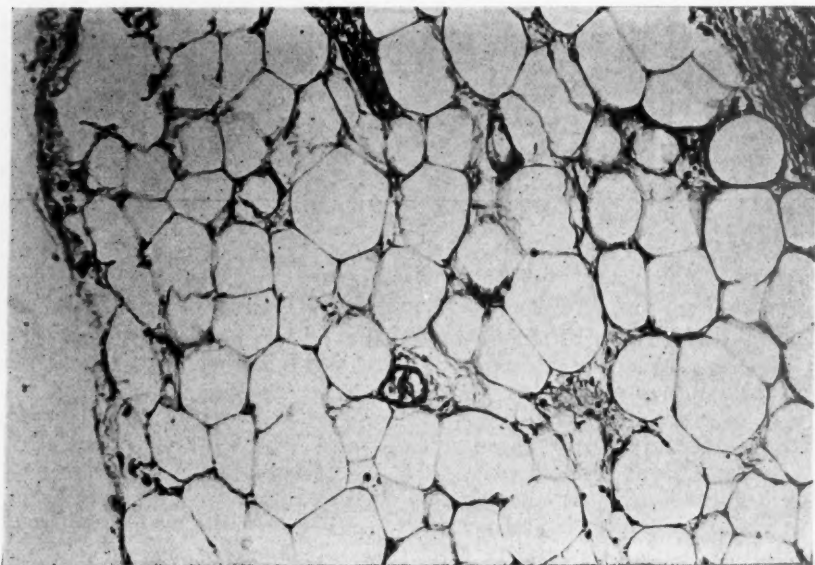


Fig. 1.—Control. Perirenal fat with trauma from a pouch formation and no sulfanilamide powder. Demonstrates mild inflammatory reaction and some regeneration of fat cells. Ten days postoperative.

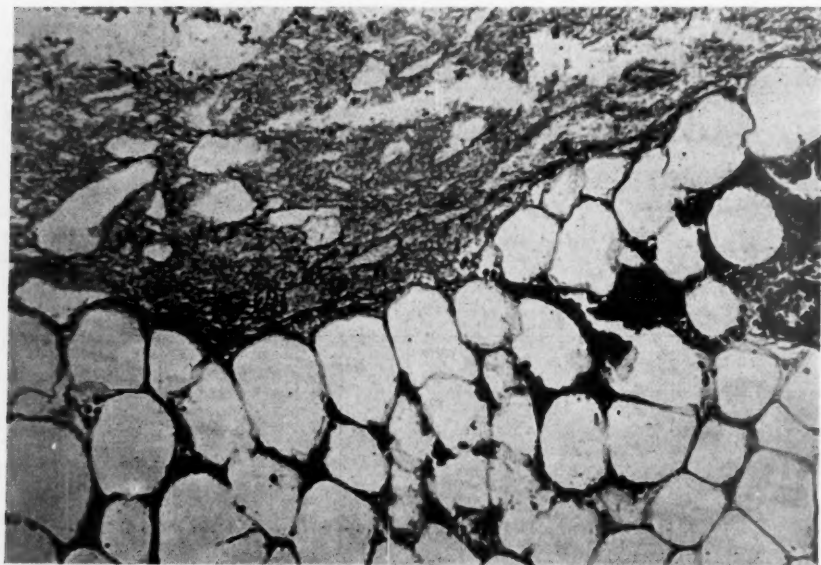


Fig. 2.—Pouch in perirenal fat with sulfanilamide powder introduced. Demonstrates fat necrosis with inflammation, exudate, and no evidence of regenerating fat cells, ten days postoperative.

of control pouches were made. We found that it took seven days for the powder to be absorbed here. The reaction encountered was striking in that where sulfanilamide was buried in the fat, a marked necrosis took place. Large amounts of serosanguineous fluid was found in the

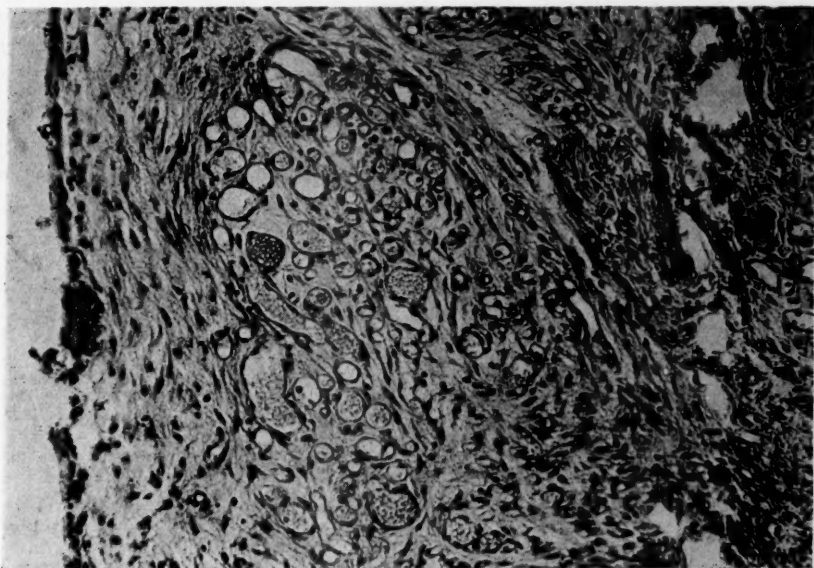


Fig. 3.—Control. Peritoneal pouch. Demonstrates dilatation of capillaries and very mild inflammation. Two days postoperative.



Fig. 4.—Peritoneal pouch with sulfanilamide powder. Histology much like control in Fig. 3. Two days postoperative.

abdominal cavity and a marked generalized peritoneal reaction noted. All ten of the group demonstrated this reaction.

5. In the peritoneal cavity we observed frequent injuries to the small intestinal walls with resultant capillary oozing. Areas thus traumatized would stop bleeding when sulfanilamide powder came in contact with them. Thus it was that we investigated further the possible styptic action of this material by taking long strips (approximately 80 cm.) of serosa off the intestinal walls and sprinkling powder over the raw oozing surfaces. Of 8 control animals, 3 died of blood loss and peritonitis, while none in a group of 12 where sulfanilamide was used died of this cause (Tables II and III). All but one rabbit in the control group developed multiple adhesions while 50 per cent demonstrated this in the sulfanilamide series.



Fig. 5.—Undissolved sulfanilamide powder, showing exudate and crystals in perirenal fat. Six days postoperative.

#### DISCUSSION

We feel that there are several points brought out here which are of clinical significance. Certainly fatty tissue does not tolerate sulfanilamide as it causes necrosis. This is in keeping with a recent statement made to us by R. C. McElroy of the Philadelphia General Hospital, "That where sulfanilamide is used in the incision and closed without drainage, 80 per cent of the wounds break down." T. L. Montgomery using sulfanilamide in the retrovesical space at low cesarean section noted a clinical picture similar to what we obtained in corresponding areas in the rabbit; i.e., fat necrosis with marked peritoneal irritation.

Sulfanilamide in the peritoneal cavity causes no reaction and is readily absorbed. This we have found true clinically.



There seems to be a local styptic action to the powder when applied to an oozing capillary bed. This observation we have found true in pelvic inflammatory disease and endometriosis.

From our studies on the rabbit, sulfanilamide did reduce the incidence of adhesions 50 per cent.

#### CONCLUSIONS

1. Sulfanilamide is safe for use in the peritoneal cavity and is absorbed quickly.
2. Sulfanilamide when used in fatty tissue causes necrosis and typical foreign body response.
3. There is a local styptic action on capillary oozing by sulfanilamide powder.
4. Experimentally there is a reduction in the incidence of adhesions.

5123 WAYNE AVENUE

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#### MACROCYTIC HYPERCHROMIC ANEMIA OF PREGNANCY\*

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**M**ACROCYTIC hyperchromic anemia induced by pregnancy is a rare disease which is believed to be the result of a deficiency of the erythrocyte maturing factor. When it occurs it may present symptoms of the utmost gravity. It is infrequent in temperate climates, but is prevalent in India, where dietary deficiencies are common. The clinical picture begins insidiously with lassitude, dyspnea, palpitation, and pallor which manifest themselves during the last trimester of pregnancy. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are frequently present. Temperature occurs in about 80 per cent of the cases. Severe symptoms may appear very suddenly, the patient going into collapse and becoming moribund. This may occur just preceding, during, or after delivery. Frequently the symptoms may be mistaken for internal hemorrhage. Retinal hemorrhages are common.

Macrocytic hyperchromic anemia may recur in subsequent pregnancies and be more severe. The maternal mortality in untreated cases is often as high as 90 per cent. If the disease is recognized and proper treatment instituted, the prognosis for both mother and child is good.

This is the first recognized and treated case of macrocytic hyperchromic anemia induced by pregnancy in approximately 18,000 deliveries at the Morrisania City Hospital.

Mrs. M. C., a 29-year-old white, Irish born housewife, para iii, gravida vi at term with no prenatal care, was admitted to the obstetric service of the Morrisania City Hospital on Sept. 8, 1941.

\*Presented at a meeting of the Obstetrical Section of the New York Academy of Medicine, November 25, 1941.

Her chief complaints were increasingly evident pallor, failing strength, and breathlessness on exertion.

One week before admission she was suddenly seized with sharp, intermittent lower abdominal pains unassociated with either bleeding or vomiting. An ambulance was summoned. The interne prescribed a sedative for what he diagnosed as a gastrointestinal upset, advised her to remain in bed, and referred her to the prenatal clinic. The severity of the pains diminished in character and degree, and finally subsided two days later. Although she remained in bed for the rest of the week, she became aware of an increasing pallor and found herself so weak that she could barely lift her head from the pillow. Becoming greatly alarmed at her progressively failing strength, she recalled the ambulance and was admitted to the hospital.

A review of her past obstetric history revealed two normal full-term pregnancies (1932 and 1933); two abortions induced by emmenagogues (1935 and 1936); and another full-term pregnancy in 1939. Her second pregnancy was associated with mild hypertension and ankle edema. Her past medical and surgical history was irrelevant.

On examination the patient answered questions coherently; she was comfortable, but her appearance was waxy; she resembled one who had sustained the loss of a large amount of blood; her lips and conjunctival mucous membranes were white, her eyes were glassy and sunk deeply in their sockets; the skin was moist but not cold, and there was a fetid odor to her breath. The pulse was rapid, 120, regular and of good quality; respiration 22; blood pressure 130/80; oral temperature 98.6° F. Two small retinal hemorrhages were discernible close to the outer border of the left disc. There was no evidence of glossitis. The heart sounds were of good quality and the lungs were clear. The abdomen was soft and not tender. A small ecchymotic area was seen in the hypogastrium. The liver and spleen were not palpable. The uterus was enlarged to the size of a full-term gestation, was soft, and presented no point of tenderness. The fetal parts were easily palpable and disappeared during a Braxton Hicks contraction. The vertex presented in the left occipitoanterior position and was unengaged. The fetal heart sounds were good. Rectal examination revealed an uneffaced soft cervix. There was no evidence of external bleeding. Slight pitting pretibial edema was present. The knee jerk and ankle jerk reflexes were normal.

Laboratory data on admission revealed: Hg, 18 per cent; red blood count, 850,000; white blood count, 5,500; hematocrit, 12 per cent; total serum protein, 4.9 (Kagan). A catheterized specimen of urine was clear yellow; specific gravity was 1.016, and contained 4-plus albumin and numerous coarsely and finely granular casts. Tests for sugar and acetone were negative.

Obstetric emergencies such as ablatio placentae, placenta previa, or ruptured uterus were considered and excluded by the quality of the pulse, the normal blood pressure, the absence of any abdominal signs or external bleeding, the softness of the uterus and the viability of the fetus.

The most pressing need for the patient at the moment was the immediate administration of blood. Fourteen hundred cubic centimeters of citrated blood were given within a period of fourteen hours. One hour before completion of the transfusion, blood specimens were taken by Dr. B. S. Kahn, hematologist. His report follows: "Hg, 33 per cent

(5.2 gr.); red blood count, 2,100,000; white blood count, 4,200; hematocrit, 18 per cent; reticulocytes, 0.2 per cent; color index, 0.8; volume index, 0.99; neutrophilic polymorphonuclears, 58 per cent; lymphocytes, 40 per cent; monocytes, 2 per cent. The red cells show many oval macrocytes, moderate anisocytosis and poikilocytosis, occasional polychromasia. It must be noted that the indices are not a reliable index of the type of anemia, as the blood examined was withdrawn during transfusion after 1,300 c.c. had entered her circulation. The smear is characteristic of that found in hyperchromic macrocytic anemia. The number of oval macrocytes, the degree of poikilocytosis, and the presence of many hyperlobed polymorphs are significant of an erythrocyte maturing factor deficiency."

At the termination of the transfusion her condition was greatly improved; temperature, 99.4° F.; pulse, 90; and respiration, 20. The blood pressure rose to 140/100, and the patient developed a moderate edema of the face and ankles. Fifty cubic centimeters of a 50 per cent glucose solution were given intravenously to promote diuresis.

The patient was questioned further to determine the etiologic factors responsible for the marked anemia. It was then elicited that she had had severe nausea associated with occasional vomiting, beginning in the second month of gestation. Her distress was only alleviated by abstaining from her usual diet and partaking of small quantities of cereal, vegetables, and milk. During the last two months she subsisted entirely on two glasses of milk and water daily. The total weight gain during her entire pregnancy was three pounds. From the onset of her pregnancy she observed ever increasing lassitude, weakness, and dyspnea in the performance of her daily household duties. At no time had there been any hematemesis, melena, or hemorrhages from any other orifices; nor did the patient complain of headache, sweats, or chills. No drugs had been taken.

From the facts thus far established, a diagnosis of a severe grade of macrocytic anemia was made. It was necessary to determine whether or not the anemia was of the pernicious type. Accordingly, a gastric analysis and a sternal tap were performed. The gastric analysis revealed normal amounts of combined and free hydrochloric acid curves. The sternal puncture was reported by Dr. B. S. Kahn as follows: "Myelocytes, 11.4 per cent; immature polymorphonuclears, 48.6 per cent; mature polymorphonuclears, 9.2 per cent; megaloblasts, 12.4 per cent; erythroblasts, 5.8 per cent; normoblasts, 12.6 per cent. Myelogram is typical of that seen in erythrocyte maturing factor deficiency anemia. It confirms the diagnosis of macrocytic anemia of pregnancy." It could now be definitely stated that the anemia was of dietary origin.

On Sept. 9, 1941, twenty-four hours after admission, the patient was placed on a high caloric vitamin B diet and given 15 units of parenteral liver extract daily. Under this treatment she showed steady improvement. She gained in strength, became more alert, color appeared in her cheeks and lips, her appetite increased, and the edema disappeared.

Additional laboratory studies within the next few days were as follows:

Urine: sp. gr. 1.016, trace of albumin, few granular and hyaline casts

Urine concentration was poor, sp. gr. 1.008, 1.012, 1.010

Blood urea clearance: 22.8 ml. of blood cleared in one minute, 41.3 per cent of normal

Wassermann: negative

Blood chemistry: blood sugar 85 mg. per 100 c.c.  
urea nitrogen 12 mg. per 100 c.c.  
uric acid 7.2 mg. per 100 c.c.

Stool examination: negative for blood and *Dibothyocephalus latum*

Blood count: (9/12/41) Hg 45 per cent, red blood count 2.2 million, white blood count 9,400

Reticulocyte count showed an excellent response to the specific therapy:

9/11/41	0.1%
9/12/41	0.1%
9/13/41	1.0%
9/15/41	9.0%
9/16/41	25.0%

On September 17, nine days after admission, at 5:30 A.M., she was abruptly awakened by a severe chill lasting fifteen minutes, associated with headache, malaise, vomiting, marked pain in the right loin, and a temperature of 104° F. Within the next twelve hours she had two more severe chills and with the last, her temperature rose to 107.6° F. There was exquisite tenderness in the right costovertebral angle. A catheterized specimen of the urine showed acid reaction, sp. gr. 1.014, negative for sugar and acetone, 1+ albumin, with moderate number of white blood cells and occasional red blood cells. A blood culture taken at the height of this chill was later reported negative. A diagnosis was made of acute pyelonephritis complicating pregnancy.

Because of this acute episode, a Watson induction was started the following morning. Two milligrams of vitamin K were given as a prophylaxis for hemorrhage. Labor began after 3 minims of pituitrin. After four and one-half hours of strong active pains, a four-pound fourteen-ounce, normal-living male child was born spontaneously. The placenta and membranes were expressed intact. The uterus remained firm. The total blood loss was approximately 100 c.c.

Immediately after delivery the temperature of the mother was 101.6° F., pulse 122, respiration 26, blood pressure 140/90. A blood count taken one-half hour post partum indicated Hg 52 per cent (8 Gm.); red blood count, 2.4 million; white blood count, 10,200; hematocrit, 25 (Wintrobe); color index, 1.1; and volume index, 1.14.

For the first five post-partum days, her temperature fluctuated between 101° and 103° F. She was fairly comfortable and had no complaints. Albumin and a moderate number of pus cells could still be found in the urine. Hexamine and sodium acid phosphate were resorted to for urinary antisepsis. The sulfonamide drugs were not used for fear of depressing hematopoiesis. With the persistence of the temperature and recurrence of chills, the hexamine was discontinued and sulfathiazole substituted. At about the same time ureteral catheterization and retrograde pyelography were done. There was no apparent obstruction in either ureter. Indigo carmine appeared from both ureteral orifices in five minutes. The urine from the right kidney revealed 40 pus cells per high power field. The left side was normal. Cultures from both sides were positive for *B. coli*.



The report of the retrograde pyelogram read: "A moderate dilatation and distention of the right kidney pelvis in the upper half of the right ureter. There appeared to be a fixed point of narrowing in the upper third of the right ureter, which may have represented the crossing of a vessel at this point. The left kidney pelvis, calyces, and ureter appeared to be normal."

Within twenty-four hours after the cystoscopy and use of sulfathiazole, the temperature dropped to 97° F. and remained normal. Sulfathiazole had no effect on the blood picture and was discontinued after five days because of the normal temperature.

The patient's appetite improved, she gained in strength and was completely relieved of all her symptoms. She was allowed out of bed on the seventeenth post-partum day and discharged three days later, at which time her blood count showed: Hg, 9.7 Gm. (62 per cent); red blood cells, 3.1 million; hematocrit, 35 per cent; color index, 1.0; volume index, 1.2. The smear still showed moderate macrocytosis. Anisocytosis less marked. Very few poikilocytes present.

A blood count of the baby taken on the first neonatal day revealed hemoglobin, 22 Gm.; red blood count, 5.4 million; white blood count 14,000. "The smear shows normal red blood cells. No abnormal white cells seen." The baby weighed 6 pounds at the time of the mother's discharge. This was a net gain of 1 pound 2 ounces in three weeks.

#### DISCUSSION

Macrocytic hyperchromic anemia is produced by a deficiency of the erythrocyte maturing factor that is usually formed in the stomach. This hematopoietic principle results from an interaction between an intrinsic factor present in the stomach and an extrinsic factor present in the protein of the diet.

Two facts prove that the above case was one of a nutritional deficiency anemia, namely, the deficient diet, and the reticulocyte response to the specific liver therapy. On admission it was postulated by the medical consultant that the clinical picture was the result of a pre-existent chronic nephritis, in view of the history of hypertension and edema in a previous pregnancy, and albuminuria and casts in the current pregnancy. However, it is well known that renal decompensation will result from the poor nutrition of the kidney cells by the markedly anemic blood, where the hemoglobin content is 30 per cent or less. The function of the kidney tubules depends on a high oxygen concentration in the blood, and where there is a deficiency, as in severe anemia, degenerative changes in the renal epithelium result with the appearance of albuminuria and casts.

Macrocytic anemia of pregnancy is hematologically identical with Addisonian anemia, but unlike the latter, almost always shows free hydrochloric acid in the gastric secretion and will often clear up spontaneously after delivery.

In mild cases of macrocytic hyperchromic anemia, specific liver therapy and a high vitamin B diet are sufficient, but in the more severe cases a blood transfusion is indicated because of the exigencies of labor.

#### SUMMARY

1. A case of a severe grade of macrocytic hyperchromic anemia induced by pregnancy is presented.



2. It was recognized and successfully treated with blood transfusion and parenteral liver therapy.
3. A living male child was delivered spontaneously.
4. A blood count of the child revealed no abnormalities.

We are indebted to Dr. Harry Aranow, Director of Obstetrics, for the privilege of reporting this case.

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### USE OF MERCUROCHROME TO AVOID POSTOPERATIVE CATHETERIZATIONS

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THE prevention or reduction of postoperative catheterizations in a large, active gynecologic service has always been a problem of considerable importance. This is especially true in a charity hospital where prolongation of stay due to bladder or kidney infections, results in a greater cost and a decided decrease in the turnover of patients.

On the Tulane gynecologic service at the New Orleans Charity Hospital, this problem has persisted and we have attempted to combat it by the usual means, such as retention catheters, or routine catheterization after voiding until the residual urine is less than one ounce. The use of urinary antiseptics preoperatively has also been tried. None of these measures have resulted in any material decrease in the number of postoperative bladder and kidney infections.

In the early part of 1940, I began the use of mercurochrome instillation into the urinary bladder as described by Woodruff and Te Linde. The technique was as follows: Instillation of one ounce of 0.5 per cent aqueous solution of mercurochrome into the urinary bladder as soon as the operative procedure is completed and before the patient is removed from the operating room.

A total of 114 patients, upon whom various gynecologic operative procedures had been carried out, were managed in this manner, and, as is shown in Table I, 93 (81 per cent) did not require catheterization.

There were 23 (19 per cent) who did require catheterization, and of this number, there were 11 who were catheterized only once, following instillation of mercurochrome. Many of the patients had a desire to void shortly after reacting from the anesthetic, and quite a few did void at this time. Very few of these required catheterizations at a later time. Inhalation anesthesia was used in all but one case.

TABLE I. RESULTS IN TREATED CASES

Total number of cases	114
Total number of voiding	93 (81%)
Total number catheterized	23 (19%)

In a control series of 97 patients handled by the author at the same hospital, there were 45 (47 per cent) who voided normally, while 52 (53 per cent) required catheterization. The routine postoperative care in this series was catheterization every eight to ten hours when necessary (Table II). These results compare well with those reported by Woodruff and Te Linde and are, as they stated, higher from the standpoint of number requiring catheterization than in many other series that have been reported in the literature.

TABLE II. RESULTS IN UNTREATED CASES

Total number of cases	97
Total number of voiding	45 (47%)
Total number catheterized	52 (53%)

In general, it is well established that catheterization is more frequently necessary when extensive operative work is done about the region of the urinary bladder. With that in mind we have grouped them according to the operation performed, so as to determine the value of mercurochrome instillation in those having surgery about the bladder.

Among the treated patients, there were 28 on whom a laparotomy only had been performed, and of these there were 23 (82 per cent) that voided normally; 5 required catheterization. Of the 12 total hysterectomies in this series, only 3 had to be catheterized. The various operative procedures are shown in Table III.

TABLE III. OPERATIONS IN TREATED LAPAROTOMIES

Total abdominal hysterectomy	12 cases
Supravaginal hysterectomy	1 case
Uterine suspensions and appendectomies	15 cases

In the control series there were 30 laparotomies; 22 (73 per cent) voided normally, while the remaining 8 were catheterized one or more times. Table IV shows the type of operation in these cases.

The amount of urine voided and the time interval between operation and voiding is of considerable interest. In the 23 treated patients who

TABLE IV. OPERATIONS IN UNTREATED LAPAROTOMIES

Total abdominal hysterectomy	12 cases
Supravaginal hysterectomy	4 cases
Uterine suspensions and appendectomies	14 cases

voided, the average amount was 162 c.c., and the average time post-operatively of the first voiding was five hours and twenty minutes. For the untreated cases, of the 22 that voided normally, the average amount was 168 c.c., and the average time for first voiding was eight hours. These results confirm the findings of Woodruff and Te Linde and show that by means of this simple procedure the treated patients in five and one-half hours voided as much as did the controls in eight hours.

There were 39 patients in the treated series who had both a vaginal plastic and a laparotomy, and of these there were 34 (87 per cent) who voided spontaneously (17 had had a total abdominal hysterectomy). In the controls there were 23 cases, 11 (47 per cent) of whom voided. This series although smaller in number does indicate the efficacy of this procedure. These figures and the type of operation are shown in Tables V and VI.

TABLE V. OPERATIONS IN TREATED VAGINAL PLASTICS AND LAPAROTOMIES

Vaginal plastic and total abdominal hysterectomy	17
Vaginal plastic and abdominal uterine suspension	18
Vaginal plastic and salpingectomy	4

TABLE VI. OPERATIONS IN UNTREATED VAGINAL PLASTICS AND LAPAROTOMIES

Vaginal plastic and total hysterectomy	9
Vaginal plastic and abdominal uterine suspension	7
Vaginal plastic and salpingectomy	7

The average amount of urine voided by the patients who were treated and had a vaginal plastic and laparotomy was 167 c.c., and in the untreated ones was 148 c.c. The average time of voiding in the treated patients was five hours and twenty minutes, while in the untreated ones it was ten hours. These figures show again that in the treated patients the bladder was more completely emptied in a considerably shorter time, thus preventing the occurrence of stasis and the resulting bladder infection that so commonly follows.

There was a total of 47 treated patients on whom various types of vaginal plastics were done, and 36 (76 per cent) voided following surgery and 11 (24 per cent) required one or more catheterizations. Of the 36 that voided, there were 24 on whom extensive work was done about the urinary bladder, most of them having a vaginal hysterectomy. Among the controls, of 44 cases there were 17 (40 per cent) that voided, while 27 (60 per cent) required one or more catheterizations. These figures do show that this procedure is of value where extensive vaginal

plasties are done. The type of operation performed is shown in detail in Tables VII and VIII.

TABLE VII. OPERATIONS IN TREATED VAGINAL PLASTICS

Vaginal hysterectomy and anterior and posterior colporrhaphy	16
Manchester operation	7
Anterior colporrhaphy and urethroplasty	10
Cervical operations	9
Dilatation and curettage	5

TABLE VIII. OPERATIONS IN UNTREATED VAGINAL PLASTICS

Vaginal hysterectomy and anterior and posterior colporrhaphy	20
Manchester operation	7
Anterior colporrhaphy and urethroplasty	12
Cervical operations	7
Dilatation and curettage	1

The average amount voided by the treated patients having a vaginal plastic was 186 c.c. which is more than that voided by those having a laparotomy. In the untreated ones, the average amount was only 70 c.c. or two and one-half times less than in the treated ones. The average time of voiding in the treated patients was six hours and forty minutes while in the controls it was seven hours.

There were three complications among the 114 treated patients. The most serious one was that of pelvic peritonitis which followed the removal of a cervical stump. After a rather stormy course the patient made a complete recovery. The second complication was one of gross hematuria that occurred on the second postoperative day in a patient that had a Manchester operation and perineorrhaphy. This condition was treated by means of bladder irrigations, using boric acid solution, and was completely cured after two days. The third was that of cystitis in a patient on whom a Le Fort colpocleisis had been done. This condition developed on the third postoperative day, and it is interesting to note that she had voided 100 c.c. shortly after surgery, but was catheterized on the third postoperative day after voiding and was found to have 150 c.c. of residual urine present. The presence of this residual urine undoubtedly contributed to the development of her infection. A complete recovery was made following bladder irrigations and urinary antiseptics.

In the untreated patients there were 15 who developed clinical cystitis from among the 97 who were operated upon. Every one of these were catheterized postoperatively. In 9 instances, the patients had had an extensive vaginal plastic and in 6 a vaginal plastic and a laparotomy. Pyelitis did not develop in any of these patients. These figures seem to indicate that bladder infections occur less frequently in the treated group.

## SUMMARY AND CONCLUSIONS

One hundred and fourteen patients on whom various gynecologic operative procedures were performed received a bladder instillation of 1 ounce of a 0.5 per cent aqueous solution of mercurochrome, postoperatively to avoid catheterization, and of these, 93 (81 per cent) voided spontaneously. In 97 untreated patients handled by the same surgeon, only 45 (47 per cent) voided normally. In the instance where a laparotomy only was done, 82 per cent voided normally in the treated group, while in the controls there were only 73 per cent. The treated patients who had laparotomies voided as much urine in five and one-half hours as did the controls in eight hours; demonstrating that by the use of this simple aid the patient was able to more completely empty the bladder in a shorter time.

Among the treated patients who had both a vaginal plastic and a laparotomy, 87 per cent voided, as compared with 47 per cent in the untreated ones. They also voided more urine in five hours than did the controls in ten hours.

For those having a vaginal plastic, 76 per cent voided among the treated group, while among the controls only 40 per cent. Here again more urine was passed in the treated group and in a shorter time.

Among the treated patients there were three complications, while in the controls 15 patients had complications; all being cystitis.

This simple procedure has, in the author's opinion, brought about a more comfortable convalescence with fewer complications and is now used routinely on his service.

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Byron, F. X., and Welch, C. Stuart: A Complication From the Use of Glove Powder, Surgery 10: 766, 1941.

Nodules in operative scars sometimes present interesting problems. Commonly, they are due to malignant implants or metastases or foreign bodies, such as suture material. In some cases, tuberculosis or endometriosis is found. In this communication the writers call attention to the importance of talcum powder as a causative factor not only of nodules in skin and subcutaneous tissue of abdominal incisions but also of tubercle-like lesions of the peritoneum. During the last year, the authors have observed several such instances. Small nodules, often tender to pressure or even painful, were discovered consisting of miliare granulomatous lesions resembling tubercles. They describe in detail four cases and offer several microphotographs showing the histopathologic pictures of foreign body giant cells containing talc crystals.

It seems obvious that gloves after being put on should be carefully washed in a hand basin.

HUGO EHRENFEST.



## TREATMENT OF HYPEREMESIS GRAVIDARUM WITH INTRAMUSCULAR INJECTIONS OF HUSBAND'S BLOOD

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**H**YPEREMESIS gravidarum may vary from a moderately annoying condition to a very serious one in which it becomes imperative to interrupt pregnancy to insure the safety of the mother. Treatment is usually moderately effective, yet the occasional case arises in which the accepted methods of treatment fail. The purpose of this presentation is to present a case which was almost completely relieved of nausea for the first thirty-six weeks of gestation by means of intramuscular injections of the husband's blood, after various other methods of treatment in seven previous pregnancies had failed to control it. The result was striking and no other treatment was instituted or necessary. It is hoped that this report will stimulate further investigations to determine the active factor.

The stimulus for the trial of this method was twofold: (1) The fact that each time after intercourse at night the patient awakened in the morning with a headache similar to that which she experienced from eating certain foods to which she was sensitive, and this fact led to the suspicion that she might be sensitive to all the tissues of her husband. It was thought that the developing tissues of the fetus following the husband's characteristics also might be incompatible with the mother and that the severe hyperemesis might be a response to this tissue incompatibility. The fact that the patient was a universal donor was also suggestive, although this has not been borne out by subsequent cases. It was not beyond the realm of possibility that intramuscular injections of the husband's blood might stimulate the formation of products that would counteract this "tissue sensitivity." (2) The fact that a report from Dr. L. C. Purvis<sup>1</sup> of Westboro, Ontario, in which he stated that he had treated 15 cases of pernicious vomiting of pregnancy with injections of the husband's blood. He used three injections of blood at intervals of three days, the first two being 5 c.c. each and the third being 10 c.c. He said the vomiting ceased in every instance.

### CASE REPORT

The first pregnancy occurred when S. A. H. was 25 years of age. Extreme nausea and vomiting began two weeks after conception and continued unabated despite injections of corpus luteum, intravenous glucose, and calcium until the twenty-eighth week, Feb. 12, 1930, when a vaginal hemorrhage of uterine origin occurred followed by a miscarriage. The prostration was so severe that she was not able to be out of bed during any part of the pregnancy. The premature baby died in three days from multiple hemorrhages. In the mother acidosis was marked, and there was a weight loss of thirty-five pounds, making her weight 110 pounds.

Second pregnancy occurred eight months later, October, 1930. After two weeks, nausea and vomiting became severe and at the end of six weeks the pregnancy was terminated by a curettage. As in the previous and subsequent pregnancies, vomitus consisted of almost pure bile and nothing taken by mouth could be retained. Corpus luteum, intravenous glucose and calcium were given during the pregnancy with little effect.

On Feb. 25, 1933, a myomectomy for fibroma of the uterine wall was performed because of irregular menses and metrorrhagia. It was about the size of a small grapefruit.

Third pregnancy was accompanied by the same extreme nausea and vomiting of lemon-colored fluid. A spontaneous miscarriage took place at the twenty-fourth week, Dec. 27, 1935. The weight loss was moderate and nothing was retained by mouth unless lobster was taken during the meal. Thyroid was given during this pregnancy and also proluton with little effect on the nausea.

Fourth pregnancy was similarly accompanied by extreme nausea and vomiting with prostration, and ended at the fourth month (April 14, 1936) in spontaneous miscarriage.

Fifth pregnancy followed a similar stormy course, ending on Dec. 24, 1936, at eleven weeks in spontaneous abortion.

Sixth pregnancy: Extreme nausea and vomiting began at the second week as in previous pregnancies. During this pregnancy proluton was given and also insulin twenty minutes before the evening meal. Atropine sulfate was also given by mouth. As with other pregnancies the patient was constantly confined to bed, being able to retain some evening meals, but never anything before 2 P.M. except white radishes, which were found to reduce the nausea considerably. Weight loss was less, but at the twenty-fourth week spontaneous miscarriage took place, July, 1938. Moderate doses of wheat germ oil, 30 drops, twice daily, and wheat germ, one tablespoon, twice daily, were given during this pregnancy. The wheat germ was tolerated better than the oil, which increased the nausea.

Seventh pregnancy: Vomiting began at the fourth week and was extreme. A few evening meals in which lobster was included were retained. Proluton,  $\frac{1}{2}$  mg., was given intramuscularly daily from the second to the fifth month and twice weekly subsequently. The severe vomiting continued until a spontaneous miscarriage took place at the twenty-eighth week, June 18, 1939.

In each of the preceding seven pregnancies, the vomiting began during the first month and was extreme with moderate to considerable weight loss with only an occasional evening meal retained. The vomitus consisted for the most part of clear lemon-colored bile. Sometimes food was retained for several hours, there being apparently a lack of gastric peristalsis with a spastic condition of the pylorus which later was confirmed by fluoroscopic examination. Food taken late one day would often be brought up the next morning.

In the eighth pregnancy, however, there was a complete change, due, apparently, to a different method of treatment.

Injections of 2 c.c. of the husband's blood were given intramuscularly at intervals of from two to fourteen days, throughout the pregnancy.

This method of treatment was further suggested by the incompatible blood grouping of husband and wife in the present instance, since the

wife was a universal donor and the husband belonged to Group A (international classification). It was thought that the blood (or other tissues) of the developing fetus might be incompatible with the mother, and that intramuscular injections of the husband's blood might help to neutralize the effect on the mother of the developing tissues (probably the blood in particular). The effect was usually evident within an hour of the injection.

Eighth pregnancy: Nausea similar to previous pregnancies began about the fourth week after conception. On Sept. 23, 1940, 2.5 c.c. of the husband's blood were given intramuscularly one evening. The next morning the patient was able to get up and have breakfast for the first time in a week. The relief lasted about six days when mild nausea re-

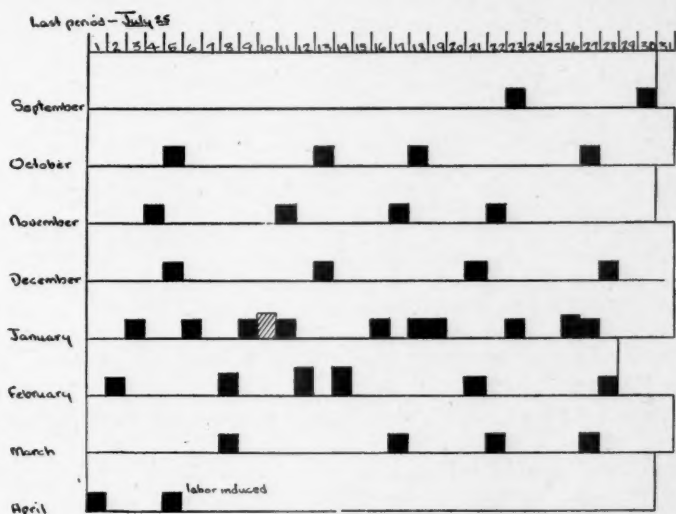


Fig. 1.—Husband's blood given intramuscularly in doses of  $2\frac{1}{2}$  to  $3\frac{1}{2}$  c.c. as frequently as necessary, depending on the patient's symptoms. Each square represents one injection. The crossed square, January 10, represents  $3\frac{1}{2}$  c.c. of patient's own blood.

turned. A second dose on September 30 brought similar relief. It was found necessary to repeat the injections every three to eight days, throughout the entire pregnancy, the longest interval being two weeks (Fig. 1).

The relief was striking and constantly repeated with each dose. It did not seem to make any difference what time of day it was given. When given while the patient was up and about, the effect was noticeable within an hour or two. The patient did have some heartburn which was not relieved by the blood injections.

Having seen two articles in which autohemotherapy<sup>6,7</sup> was reported as giving relief from the nausea of pregnancy, it was decided (for one of the injections) to substitute 3 c.c. of the patient's own blood for the husband's to determine if this would give relief. No relief followed this injection, so the next day 2.5 c.c. of the husband's blood were given with relief that lasted five days.

The pregnancy advanced to the twenty-first week, Jan. 3, 1941, when a miscarriage was threatened. There were severe rhythmic uterine con-

tractions. This was controlled by luminal sodium, 5 gr., and proluton, 0.2 mg., given intramuscularly and codeine 2 gr. subcutaneously. It was necessary to repeat this procedure three times subsequently, January 5, 29, and February 12.

The patient was able to be up and about throughout all but the last six weeks of the last pregnancy which was in striking contrast to the seven previous gestations. She even took several train, car, and plane trips, totaling almost 4,000 miles during the second and third months of gestation. At the thirty-sixth week the patient began to feel badly and the blood pressure rose from the usual 100/70 to 120/80 with general malaise and mental depression. The urea in the blood was slightly elevated, and it was thought that the patient was threatened with an atypical toxemia. Labor was, therefore, induced on April 5, 1941, and a well-developed female child was born April 6, 1941. The only abnormality noted was a moderate jaundice which cleared up in about three weeks.

The report on the blood groupings was as follows:

Baby's blood: 4/7/41, Taken the day after birth. Type A (international classification).

Father's blood was the same group, and there was no cross agglutination after one-half hour.

Mother's blood belonged to Group O (international classification).

The microscopic cross-agglutination test showed agglutination of daughter's cells by the mother's serum and no agglutination of the mother's cells by the daughter's serum after one-half hour. Thus, it is seen that the newly forming blood and probably other tissues of the developing fetus were actually incompatible, at least with the mother's blood.

Thinking that the Rh factor iso-immunization might account for some of the pathology, tests were carried out on the parents. It was found that the father's blood was Rh negative and the mother's and baby's bloods Rh positive, thus excluding the possibility that there could be any iso-immunization factor as a cause of the hyperemesis. Tests for another antigen, work in which is to be published shortly, were carried out. This antigen which has just been brought to light may possibly have been a factor in the present case as the father's and baby's bloods were positive and the mother's was negative.

#### COMMENTS

It is worthy of note that the patient had been allergic to certain foods for several years. She would suffer from severe incapacitating headaches requiring 2 to 3 gr. of codeine by hypodermic to control them. The headaches occurred six to eight hours after taking such articles of diet as coffee, chocolate, peas, maple syrup, and cow's milk and cream. She was extremely sensitive to paprika, having had attacks of pulmonary edema on three different occasions. These reactions were unaltered by the pregnancy, but most interesting was the fact that she began to have a return of this severe type of headache during the pregnancy without taking any food to which she was known to be sensitive. It was found that when the husband had taken any of the foods to which she was sensitive that a headache followed the injection of his blood within two or three hours. After the twentieth week, the



husband discontinued eating above-mentioned articles of diet, and the patient had no further headaches.

It is hoped that this report will stimulate further work to determine the answer to several questions:

1. Would female blood of the same group as the husband's be equally effective?
2. Would male or female blood from persons of other groups be effective?
3. Would serum or plasma of proper group but other than that of the husband produce the same result?
4. Is the active agent some hitherto unknown factor other than blood (or tissue?) group incompatibility?
5. What was the constituent of the husband's blood that caused the allergic headache in the patient after intramuscular injection of his blood when he had taken any food to which she was sensitive (histamine?)?

If female blood would relieve the patient, it would be proof that male hormone could not be a factor. If male blood of the woman's own blood group would produce the result, it could not be the specific blood group incompatibility which was the underlying cause of the distress in the pregnant woman.

The work of W. Haase<sup>2</sup> has shown that incompatible blood grouping had nothing to do with the development of eclampsia, since the blood groups of the mother, father and baby were all the same in a series of 20 unselected cases of eclampsia.

It is worthy of note that Polayes<sup>30</sup> also investigating eclampsia found that in a series of 12 cases the mother and baby were uniformly of the same blood group. The results of these two separate investigators suggest that the blood grouping may have had something to do with the development of eclampsia but the exact mechanism of the production of the toxemia is unknown. It could not have been due to A or B antigen incompatibility but to some intra-group reaction.

Since this report was first prepared, a number of obstetricians have been contacted. One tried injections of the husband's blood on four patients suffering from hyperemesis. In all of these cases the hyperemesis was controlled by the use of three or four intramuscular injections of the husband's blood. The final work on the antigen factors is still to be carried out in some cases. In some the mother was not a universal donor as in the case above reported.

It is recognized that many other methods of treatment have been reported and are effective in many cases. Some of these were tried in previous pregnancies in the above-mentioned patient, such as proluton,<sup>3</sup> intravenous glucose and insulin,<sup>4, 5</sup> autohemotherapy,<sup>6, 7</sup> various vitamins,<sup>8</sup> calcium therapy,<sup>9</sup> and wheat germ oil. Other methods advocated by various authors are variations of hormone therapy,<sup>10</sup> adrenal cortex,<sup>11, 12</sup> liver injections,<sup>13, 14, 19</sup> various vitamin injections,<sup>12, 15-19</sup> enemas of the patient's urine,<sup>20, 21</sup> psychotherapy,<sup>22</sup> adjustment of the salt balance,<sup>23</sup> administration of fibrinolysate,<sup>24</sup> histidine,<sup>25</sup> amyl-nitrate and glyceryl-trinitrate,<sup>26</sup> biliary drainage with duodenal tube,<sup>27</sup> Chinese acupuncture,<sup>28</sup> parathyroid extract with calcium,<sup>9</sup> phenobarbital, pneumoperitoneum.<sup>29</sup> The use of husband's blood was mentioned but not discussed in articles by LeFevre,<sup>5</sup> Saxon and Stoll<sup>6</sup> and also reported on by Thierry,<sup>31</sup> who used serum in five cases, Canouet<sup>32</sup> and W. S. Horn.<sup>33</sup> Treatment by injections of husband's



blood is not mentioned in any of the recent textbooks on obstetrics although Kosmak,<sup>37</sup> in 1922, made reference to a report by Blair Bell, the original reference for which the author was unable to find.

*Additional Comment.*—It is interesting to note that the baby, now nine months of age, is extremely sensitive to cow's milk. She became pulseless, cyanotic, and went into shock when given her first tablespoonful of cow's milk at seven months of age. The reaction was repeated on a second trial of a smaller amount of cow's milk one month later.

It would seem very definite that since many other forms of treatment had been tried in 7 pregnancies that the injections of husband's blood had a decidedly advantageous therapeutic effect in this case and in other cases in which it has been tried. Although the cause of the hyperemesis and the reason for the immediate relief of symptoms are still conjectural, the fact remains that all the symptoms ceased with this simple treatment. The patient was allergic to certain foods and the baby has inherited this tendency.

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## THE USE OF ESTROGENS IN THE TREATMENT OF LEUCOPLAKIA, KRAUROSIS, AND SENILE VAGINITIS

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**P**RRURITUS VULVAE, being a symptom and not a disease, has many etiologic factors: some systemic, such as diabetes; some hygienic, such as uncleanness; and some local, such as leucoplakia and kraurosis vulvae.

It is with the local factors only that we are concerned in this discussion for, obviously, these are the only ones which might be susceptible to estrogen therapy.

Investigation of the literature discloses that there is considerable confusion concerning local diseases of the vulva and vagina, generally due, apparently, to a lack of understanding of the identities of two of the most frequent diseases of this area, leucoplakia and kraurosis.

Ever since the latter part of the last century, when Breisky<sup>1</sup> (1885) first described a disease which he termed "kraurosis vulvae," there has been vagueness as to the identity of this condition. In 1909, Bonney devoted three Hunterian lectures to a discussion of kraurosis vulvae and leucoplakic vulvitis, the disease with which it had, and has, been frequently confused, and in the same year leucoplakic vulvitis was clearly identified and described in a classic paper by Berkeley and Bonney.<sup>2</sup> To quote their original description: "Leukoplakic vulvitis is to be defined as a chronic inflammatory condition of unknown origin characterized in its early stages by marked hyperemia and cellular activity, and in its later phases by marked epithelial hypertrophy and a thickened, sclerosed and retracted condition of the subepithelial tissue. Its distribution varies with its severity and time of incidence. In a well-marked case the whole of the vulva may be implicated with the exception of the vestibule and orifice of the urethra *which are never affected*, and not only may the labia majora, minora, anterior and posterior commissures and the clitoris suffer, but the disease may even spread laterally to the folds of the thighs and posteriorly over the perineum and skin surrounding the anus."

In contrast to this, we have their description of kraurosis: "Kraurosis vulvae consists of an atrophic condition of the vulva, associated clinically with stenosis of the vaginal orifice, and pathologically with certain changes in the dermis. The labia minora, vestibule, orifice of the urethra, and that of the vagina are always affected, the hood of the clitoris sometimes. The skin on the outer surface of the labia

majora between the labia majora and folds of the thigh covering the perineum and surrounding the anus *is never affected.*"

The distribution of these lesions then is quite different, leucoplakia affecting the skin around the vulva and kraurosis affecting the mucous membrane within the boundaries of the labia minora.

The pathology of the two diseases is also quite different, leucoplakia being characterized by a swelling and hyperemia of the epithelium and later by a pronounced cellular proliferation of the subepithelial tissue. Still later the subepithelial tissue becomes fibrotic and the basal layers of the epithelium markedly hypertrophied. The continued sclerosis of the subepithelial tissue produces the characteristic smooth and shiny white appearance which may become cracked, fissured, and ulcerated.

Kraurosis, on the other hand, produces an extremely thin epithelium with atrophic papillae which in many places have almost disappeared. A retention of normal elastic tissue and a massive infiltration of white cells of all types are also identifying characteristics. This disease is much more closely akin to simple senile vaginitis and may be an aftermath of the latter and have the same etiology, i.e., estrogen depletion. A long time before the physiology of estrogens was well known, kraurosis was thought to be due to ovarian failure, and from a physiologic point of view, it would be reasonable to suppose that estrogen therapy would have a more beneficial effect on the symptoms of this disease than on those of leucoplakic vulvitis.

Since there is evidence that estrogen used as an inunction has a local effect on the tissues, it has been thought that its local application to the affected areas might be more beneficial than parenteral or oral administration.

Various estrogens have been used in inunctions for this purpose in both leucoplakia and kraurosis. As a rule, no attempts have been made recently to distinguish between these diseases, and both have been called variations of chronic atrophic dermatitis (Adair and Davis<sup>3</sup>).

Kerkovian<sup>4</sup> treated 4 patients with a salve containing 0.5 mg. of estradiol per c.c. of sesame oil base, applying 1 c.c. of the salve at two- to six-day intervals with beneficial results. A larger series of 21 patients treated with dihydroxyestrin salve was reported by Finkler and Antopol<sup>5</sup> who followed their patients with vaginal biopsies and smears. All but 6 were relieved by treatment and 1 patient, who received approximately 100,000 R.U. of estrogen by inunction in three months, developed a recurrence of uterine bleeding following the menopause.

Mishell and Motyloff, using estriol or trihydroxyestrin, noticed improvement in all of 3 patients treated. The dosage was not indicated.

Within the past two years, 21 patients complaining of pruritus vulvae have been admitted to an endocrine clinic of the Sloane Hospital for Women.

Evaluation of these cases disclosed the following diagnosis:

Senile vaginitis and kraurosis	9
Leucoplakia	7
Dermatitis venenata	1
Lichen simplex chronicus	1
Monilia infection	1
Diabetes mellitus	2
	<hr/>
	21

Those cases diagnosed as senile vaginitis, kraurosis and leucoplakia were treated. The rest were referred to appropriate clinics for further investigation.

The treatment consisted of the local application of an ointment of lanolin base containing 10 mg. of diethylstilbestrol per 30 c.c. of salve. The patients were instructed to apply about 30 c.c. of the ointment locally every day for one week. It is obvious that this could result in only an approximate daily dosage of estrogen. If improvement occurred at all, it was usually quite apparent within one week, but the treatment was tried for one month in the unimproved cases before being given up as unsuccessful. The success or failure of the treatment was based entirely on its ability to relieve the symptoms of pruritus and burning. No biopsies were made of vaginal or vulvar tissue.

Of the 9 patients in the senile vaginitis, kraurosis group, 5 were completely relieved of symptoms, 1 was improved, and 2 were unimproved. One was not treated with estrogen salve because of the presence of carcinoma elsewhere in the body.

Of the 7 patients with leucoplakia, 2 were completely relieved, 1 was improved, and 4 were unimproved.

Three of the above 16 patients have remained symptom free without further treatment after one month of inunction. The others find it necessary to resort to the use of salve once or twice a week to prevent recurrence of symptoms.

Several patients obtained relief from coincidental hot flushes during treatment, and one patient had a period of uterine bleeding following cessation of treatment. These cases indicate a systemic reaction to estrogen absorbed percutaneously, and the uterine bleeding was thought to be an estrogen withdrawal phenomenon.

#### SUMMARY

Kraurosis vulvae and leucoplakia are causes of pruritus vulvae. The differences in their distribution and pathology are discussed.

Since kraurosis is more closely akin to senile vaginitis and therefore may be due to estrogen depletion, it was thought that kraurosis might be more susceptible to estrogen therapy than leucoplakia.

Twenty-one patients complaining of pruritus vulvae are reviewed.

Sixteen of these, diagnosed as senile vaginitis, kraurosis, or leucoplakia, were treated with estrogen salve locally.

Although the series is too small for definite conclusions, there is a suggestion that estrogen therapy is more successful in the treatment of kraurosis than of leucoplakia.

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### THE USE OF METHYL TESTOSTERONE FOR THE RELIEF OF BREAST ENGORGEMENT IN THE PUERPERIUM

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IN THE past few years a number of reports have been published on the use of testosterone for the relief of breast engorgement in the puerperium<sup>1</sup> and on the inhibition of lactation.<sup>2, 3</sup> In these studies, the testosterone was administered parenterally, and the results were almost uniformly satisfactory. More recently methyl testosterone has been produced for oral administration. Realizing that the oral administration of hormonal substances is frequently ineffective, it was decided to carry out this study in order to ascertain its value, because many patients dislike injections. Except in cases of emergency an effective oral medication is to be preferred to a parenteral one.

This series consists of 50 cases. At no time during the treatment was there permitted a restriction of fluids, a reduction in diet, ice bags, saline cathartics, or any analgesics which might in any way interfere with the true evaluation of the efficacy of this medication. The cases were taken at random, some because of stillbirth, others because of unsatisfactory condition of the nipples, and still others because the mother preferred not to nurse.

In all cases, the medication was not started until the breasts were quite full, usually on the third or fourth day postpartum. This was done because it has been shown that testosterone is most effective at that time.<sup>4</sup>

During the first few days after delivery, there is still a sufficient amount of estrogen in the circulation to inhibit the pituitary from liberating its prolactin, and any testosterone given too early would be excreted without any lasting inhibitory effect. When the breasts begin



to fill, it is indicative of the fact that the supply of estrogen is so greatly diminished that it no longer prevents the pituitary from liberating its prolactin. Just how the testosterone does its work in inhibiting lactation has not as yet been proved. It might inhibit the pituitary from liberating the prolactin, or it might antagonize the lactogenic hormone itself, or it might depress the receptivity of the breast so that it cannot be stimulated by the prolactin.

Hamilton<sup>5</sup> has shown an inhibiting effect on the hypophysis as well as histologic changes from testosterone, but Reece and Mixner<sup>6</sup> employed testosterone propionate in sexually matured spayed rats, and they found that the yield of pituitary lactogen was augmented. Hence the *modus operandi* is still debatable.

In presenting Table I, the column designated "breast before treatment" is given in numbers. The number "4" represents a breast which is full, firm, tender, painful, and caked. Number "3" is a breast which has the above qualities to a lesser degree. When a breast is full but only slightly painful or tender, it was represented by the number "2."

#### DISCUSSION

The results were classified as good if the patient acquired almost complete subjective and objective relief. That is, the breasts became neither painful nor tender to touch. A small percentage of these continued to lactate to a minor degree for several days after the treatment was discontinued. But our purpose of the treatment was not to prevent lactation, but rather to cure the pain and discomfort of weaning.

Those patients who had moderate relief of pain and tenderness were designated as fair. Those patients who showed no appreciable relief were designated as poor.

There were 44, or 88 per cent, with good results, 4, or 8 per cent, fair, and 2, or 4 per cent, who had poor results.

Of the cases designated as good, there were two which require additional information. One, J. W., was a woman whose breasts were engorged and painful. She was nursing her infant. In this case, 60 mg. were given, divided into three doses. This relieved the pain and tenderness, and permitted her to nurse satisfactorily. The infant continued to gain well with the subsequent milk. The second case (F. B.,<sup>1</sup>) was a woman who developed an acute exacerbation of a chronic cholecystitis. She was given daily small doses of magnesium sulfate, and was on a restricted gall bladder diet. Therefore, it is difficult to state whether the improvement in her breasts was due to the methyl testosterone or to the diet restriction and magnesium sulfate, or to a little of both.

There were two patients who exhibited moderate hirsutism. The results were fair in one and poor in the other. Both these women had android pelvises. The voice was not deep although it was a little husky in one of them. It is possible that in those women with androgenic tendencies a much larger dose would be required to create a small effect due to the piling up of this substance in the system.

TABLE I

PT.	AGE	PARA	GRAV.	CHAR. OF DELIVERY	DAY P.P. OF 1ST. DOSE	DOSE MG.	BREAST BEFORE TREATMENT	RESULTS	INVOLUTION	COMMENT
E. A.	29	i	i	Spont.	6th	270	4	Poor	Normal	Mod. hirsutism. Breast pumped until fifth day Improved with ergotrate
M. A.	25	ii	ii	Spont.	3rd	150	3	Good	Subinvolution	
A. A.	32	i	ii	Spont.	3rd	150	4	Good	Normal	
E. A.	29	iii	iii	Low forceps	3rd	240	4	Good	Normal	
R. B.	24	i	i	Spont.	4th	90	4	Good	Normal	
F. B.	31	ii	ii	Spont.	3rd	60	4	Good	Normal	Gall bladder attack (see discussion, F. B. 1)
E. B.	30	ii	ii	Spont.	3rd	150	4	Good	Normal	Nursed baby third day
R. B.	20	ii	ii	Spont.	4th	150	3	Fair	Normal	
E. B.	23	i	i	Spont.	4th	90	4	Good	Normal	
D. B.	26	ii	ii	Spont.	3rd	240	3	Good	Normal	
F. B.	34	i	i	Low forceps	4th	150	4	Good	Normal	
F. C.	29	i	iii	Spont.	4th	150	4	Good	Normal	
C. C.	24	i	i	Spont.	3rd	270	4	Good	Normal	
C. C.	24	i	i	Spont.	4th	150	3	Good	Normal	
C. C.	27	ii	ii	Spont.	3rd	210	3	Good	Normal	
R. D.	21	ii	ii	Spont.	4th	150	4	Good	Normal	
R. F.	30	i	i	Spont.	4th	90	3	Good	Normal	
G. G.	26	ii	ii	Spont.	3rd	240	3	Good	Normal	
Y. G.	28	i	i	Spont.	4th	150	4	Good	Normal	
G. G.	24	ii	ii	Spont.	3rd	150	4	Good	Normal	
B. G.	30	ii	ii	Spont.	3rd	150	4	Good	Normal	
M. G.	25	i	i	Spont.	3rd	150	3	Fair	Normal	Small dose given Patient Med. Febrile
B. H.	23	i	i	Elec. Cesarean	4th	100	3	Good	Normal	

H.	34	iii	iii	Spont.	3rd	240	4	Good	Normal	Nursed until sixth day
H. H.	38	ii	ii	Premature 5½ mo. Spont. Breech	3rd 3rd	150 150	3	Good Good	Normal Normal	
M. I. V. M.	26 27	i i	i i	Spont. Breech	3rd 7th	150 150	3 4	Good Good	Normal Normal	
H. M. P. M.	27 24	ii i	ii i	Spont. Spont.	3rd 4th	150 150	4 4	Good Good	Subinvolution Normal	
R. M. M. N.	28 21	i i	i i	Breech Spont.	3rd 6th	150 150	4 3	Good Good	Normal Normal	
P. N. P.	30 28	i ii	iii ii	Spont. Spont.	3rd 3rd	150 150	4 3	Good Poor	Normal Normal	Filled in again after last dose
D. S. I. S.	31 23	ii i	ii i	Spont. Spont.	3rd 4th	150 90	4 4	Good Good	Normal Normal	
L. S.	21	i	i	Premature 5½ mo.	3rd	180	3	Fair	Good	Mod. hirsutism
H. S. M. S.	32 23	ii i	v i	Spont. Spont.	4th 4th	150 150	4 3	Fair Good	Normal Normal	
L. S.	29	ii	iii	Spont. (Hydrum.)	4th	90	3	Good	Normal	
P. S.	21	i	i	Spont.	5th	120	4	Good	Good	
T. T.	26	i	i	Low forceps	3rd	150	3	Good	Good	
L. T.	30	i	i	Spont.	3rd	90	3	Good	Normal	
V. V.	28	iii	ii	Breech	3rd	150	4	Good	Normal	
J. W.	27	i	i	Spont.	3rd	150	2	Good	Normal	
J. W.	24	ii	ii	Spont.	3rd	150	4	Good	Normal	
J. W.	30	iii	iii	Spont.	4th	60	3	Good	Normal	Temp. relief while nursing
J. W.	28	ii	ii	Spont.	4th	150	3	Good	Normal	
M. W.	40	i	i	Midforceps	5th	150	3	Good	Normal	
B. Z.	20	i	i	Spont.	4th	150	3	Good	Subinvolution	

In the two cases marked poor, one (E. A.<sup>1</sup>) should really be eliminated because in this patient methyl testosterone was not started until the sixth day and the patient's breasts were pumped twice daily from the second to the fifth day post partum. It has been shown that once suckling has begun, there is a reflex stimulation for further milk production, hence in this case too much was expected of the methyl testosterone.

In P.,<sup>1</sup> the second of the "poor" results, the breasts responded fairly well to the 150 mg. dose, but on the following day they filled in again.

Of the four cases designated as fair, additional information is offered. In one case (S.<sup>1</sup>), there was moderate hirsutism which was mentioned before. In another (M. G.), a very small dose was used, this being one of the early cases. If a larger dose had been employed, the results might have been more favorable, although this is conjectural.

The third case (R. B.), para ii, nursed her baby on the third day, bringing in another factor previously mentioned.

The fourth case (H. S.) was a gravida v, para ii, who had three abortions, 1 spontaneous and the other 2 induced. She was a very thin, nervous woman weighing ninety pounds when first seen in pregnancy at the fifth month. Because of her malnutrition and extreme nervousness, a basal metabolic rate test was attempted on two occasions without success; she did not cooperate well. Her infant died on the third day post partum quite suddenly. From her very make-up, there appears to have been a thyroid dyscrasia.

Since it is believed that the uteri of nursing mothers involute better than those that do not nurse, the fundus was watched particularly for subinvolution. It was noted in only three cases, or 6 per cent, of the series. Therefore, it is believed that this is negligible, since a similar number of subinvolved uteri is seen in nursing mothers.

As far as dosage is concerned, it varied from a minimum of 60 mg. to 270 mg. (one case). The dose most commonly employed by us is 150 mg. divided into 5 doses every four hours. This is approximately equivalent to 50 mg. of parenteral testosterone propionate.

The age of the patients varied from twenty to forty, and in both of these extremes the results were good, with the exception of the one case (R. B.) previously discussed. Therefore, age would seem to have no influence on the results.

Gravidity and parity also seemed to have little effect on the influence of the medication.

The type of delivery too played no role whatsoever, although this series is too small to prove this point conclusively.

#### CONCLUSION

Methyl testosterone orally supplies a very effective means of relieving breast engorgement in the puerperium. The method suggested is 150 mg. in 5 doses of 30 mg. each, every four hours, beginning on the third or fourth day post partum when the breasts are full.

#### SUMMARY

1. A study of a series of 50 cases is presented, showing the effect of oral methyl testosterone on the inhibition of lactation.
2. A suggestion as to the method of use is offered.

We wish to thank the Schering Corporation of Bloomfield, N. J., for their kindness in supplying the Oreton M, their brand of oral methyl testosterone, which has been used exclusively in this study.

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## THE RELATION BETWEEN UTERINE ACTIVITY AND REACTIVITY TO POSTERIOR PITUITARY EXTRACT DURING PREGNANCY

A STUDY OF 656 RECORDS MADE WITH THE LÓRÁND TOCOGRAPH

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THE spontaneous activity of the uterus and its reactivity to posterior pituitary extract during pregnancy have been studied in strips of uterine muscle removed from both human beings and animals, and upon the latter in vivo. As far as can be ascertained, however, neither type of movement has been studied systematically in patients.

Robson<sup>1</sup> studied activity and reactivity in strips of muscle removed from the rabbit. He found no definite type of activity at any of the stages of pregnancy investigated, and no direct relation between activity and reactivity. He measured reactivity in terms of the minimum amount of extract necessary to initiate contractions. By this method he confirmed the observations of Knaus,<sup>2</sup> that reactivity to large doses is absent in the first half of pregnancy, but is present later. The exact time at which it appeared, and the minimum amount of extract necessary to cause contraction varied from animal to animal. Once established, however, reactivity increased, and was found to be always high at parturition.

Robson observed considerable variation in the degree of reactivity of different uteri at parturition, and even in different parts of the same organ. Several times at parturition he noted high degrees of rhythmicity. He believed that the differences in reactivity which he noted were outside of the limits of experimental error.

Robson and Schild<sup>3</sup> studied the spontaneous contractions of the pregnant uterus of the cat in vivo and in vitro. In this animal they found a progressive increase in uterine sensitivity as pregnancy advanced.



Robson<sup>4</sup> registered the activity and reactivity of pieces of human uterus removed at various stages of pregnancy. No specific type of activity was discovered at any particular period, and at no stage of pregnancy investigated was there any definite degree of rhythmicity observed. High and low degrees of rhythmicity occurred both early and late in pregnancy. Tissue secured at the earliest periods reacted only to large amounts of extract, and no correlation was found between the character of the spontaneous contractions, and those inaugurated by the extract. Strips of muscle removed from different parts of the same uterus exhibited marked differences in activity, though their reactivity was substantially identical.

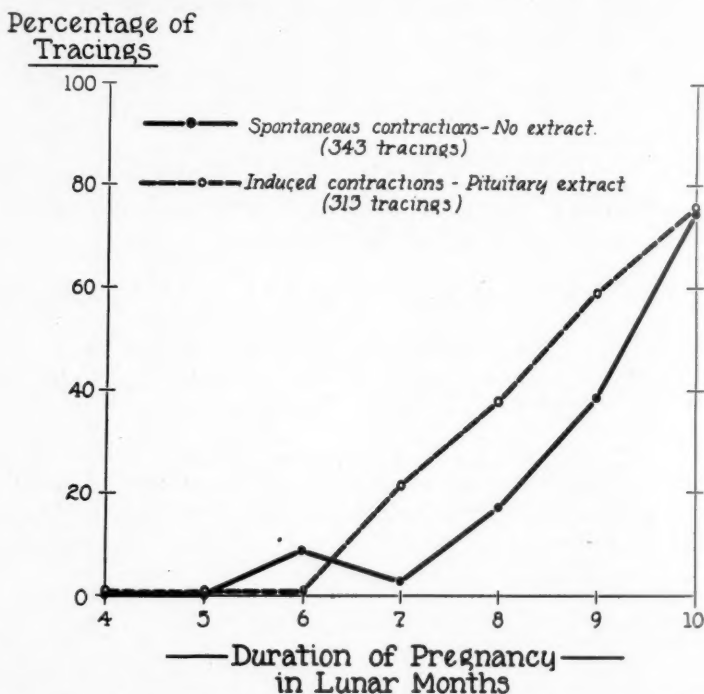


Fig. 1.—Abscissa denotes duration of pregnancy in lunar months. Ordinate indicates the percentage of tocographic tracings listed in Table I, which exhibited: (a) Spontaneously arising uterine contractions, or (b) ones resulting from the administration of posterior pituitary extract. Note parallelism in occurrence of the two types of contractions.

#### MATERIALS AND METHODS

The present observations upon activity and reactivity were made directly upon patients. Two hundred women attending the Maternity Department of the Hospital of the University of Pennsylvania supplied records of spontaneous contractions, and 32 patients residing in a Maternity Home made possible records of reactivity.

In both groups of patients the uterine contractions were registered with a Lóránd tocograph. This is a mechanical device which supplies a graphic record of uterine movements detected through the medium of the anterior abdominal wall.<sup>6</sup>

Each tracing was made with the patient in the recumbent posture, following a rest period of ten minutes. In the study of spontaneous contractions, the recording period lasted thirty minutes. The degree of activity was measured in terms of whether or not any spontaneous contractions were recorded.

Reactivity was measured in terms of whether or not the administration of posterior pituitary extract initiated contractions. In this instance the recording period lasted thirty minutes following the administration of the drug.

The patients upon whom reactivity was studied were admitted to the Maternity Home at various periods during middle and late pregnancy. Each patient was observed and tested once a week. The treatment consisted of an intramuscular injection of posterior lobe extract (obstetric pituitrin, Parke, Davis & Co.), the same dose being employed each week. Fifteen patients received a weekly dose of 3 minims, nine a dose of 2 minims and four a dose of 1 minim. Complete details of treatment and their results have been reported elsewhere.<sup>5</sup>

#### RESULTS

The number of tracings made for the purpose of registering activity and reactivity are listed in Table I, according to the duration of pregnancy. The percentages of the tracings, which registered either activity or reactivity, are shown in graphic form in Fig. 1.

TABLE 1. SHOWING THE MONTHLY DISTRIBUTION OF TOCOGRAPHIC RECORDS SECURED FROM A SERIES OF PREGNANT WOMEN, ARRANGED ACCORDING TO WHETHER OR NOT POSTERIOR PITUITARY EXTRACT WAS ADMINISTERED WHILE THE RECORDING WAS IN PROGRESS

LUNAR MONTHS OF PREGNANCY	POSTERIOR PITUITARY EXTRACT	
	NOT ADMINISTERED	ADMINISTERED
	Tracings	Tracings
4	1	1
5	6	9
6	12	12
7	38	26
8	19	64
9	44	93
10	223	108
Total	343	313

From the graph, it is apparent that activity appeared earlier in pregnancy than did reactivity. Following their onset the proportion of tracings which registered activity and reactivity increased progressively, and at the same rate of increase. More tracings recorded induced contractions than spontaneous ones. This fact no doubt depended upon the dosage of the oxytocic agent. The significant characteristic of the graph is the parallelism between the increases in activity and reactivity.

Another interesting characteristic of the graph is the observation that more than 20 per cent of the tracings in both groups, failed to register either activity or reactivity in the tenth lunar month.

## COMMENT

Robson determined the minimum amount of extract necessary to initiate contractions; since it decreased progressively as pregnancy advanced, he concluded that uterine sensitivity increased.

We found that an increasing number of patients exhibited both activity and reactivity as pregnancy advanced. We also observed at any given period in pregnancy that an increase in the dose of the stimulant made more individuals react. These observations lead us to conclude also, that sensitivity increases as pregnancy advances.

Up to the present writing we have assembled some 1,400 tocographic records of the uterine contractions of pregnancy. An analysis of this material leads to the following statements, which also confirm, to some extent, previous observations of Robson: Spontaneous uterine activity is an extremely variable quantity during pregnancy. Uterine contractions may be absent for periods as long as an hour, late in pregnancy as well as very early. Spontaneous contractions occur with great irregularity throughout the most of pregnancy, at least until the last several weeks. Exceptions have been noted, since we have observed extreme rhythmicity in the earliest tracing which we made.

Reactivity to posterior lobe extract varies widely from patient to patient both as regards the time that it first appears and in the amount necessary to initiate contractions.

## SUMMARY AND CONCLUSIONS

1. The frequency of occurrence of uterine contractions arising spontaneously, and of those contractions induced by the intramuscular administration of posterior pituitary extract was studied in a group of pregnant women, between the one hundred and tenth and two hundred and seventy-ninth day of gestation, by means of the Lóránd tocograph.

2. Spontaneous contractions were recorded for the first time during the sixth lunar month, and induced contractions during the seventh lunar month of pregnancy.

3. The proportion of records registering activity and reactivity increased progressively as pregnancy advanced, running parallel to each other.

4. From these observations it is concluded that the sensitivity of the pregnant human uterus to posterior pituitary extract increases progressively as pregnancy advances.

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## BLOOD TRANSFUSION REACTION DUE TO INTRA-GROUP INCOMPATIBILITY\*

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**R**EPEATED small blood transfusions have often proved to be life-saving measures in the treatment of chronic pelvic infections, but their use has some danger, notwithstanding blood typing and cross-matching. In the case to be reported a marked reaction developed following transfusion of blood found to be compatible by the usual laboratory methods. Further investigations revealed the reaction to be due to factors that could not be detected by these ordinary methods.

M. M. (Case No. 107616), female, white, aged 34 years, was admitted to Morrisania City Hospital on April 3, 1941. Two weeks previously a posterior colpotomy had been done at another hospital to drain a pelvic abscess. The cause of this abscess was not definitely established. She left the hospital improved but soon afterward developed a recurrence of low abdominal pains associated with chills and fever and was referred to Morrisania City Hospital.

The previous medical history was negative. Past surgery consisted of a curettage in 1938 for a spontaneous incomplete abortion. Menarche began at 14 years of age, regular, every twenty-eight days, lasting seven to eight days. The last menstrual period occurred, March 1 to 8, 1941. She had been delivered of three children; all were uncomplicated spontaneous full-term deliveries.

Physical examination revealed an acutely ill patient, temperature 105.6° F., pulse 136, and respirations 36. The skin was warm and dry. The heart and lungs showed no abnormalities. The abdomen was tense. There was marked abdominal tenderness with rebound tenderness in both lower quadrants. A profuse foul-smelling vaginal discharge was present from a healing colpotomy wound posterior to the cervix and a mass approximately 8 cm. in diameter in the left adnexal region. It was fairly firm, fixed, and extremely tender. The opposite adnexa were thickened and tender. The uterus was slightly enlarged, soft, smooth, and tender on motion.

The blood Wassermann was negative; hemoglobin, 55 per cent; red blood count, 3,140,000; white blood count, 26,000; polymorphonuclears, 82 per cent; lymphocytes, 18 per cent; sedimentation time, 18 mm. in six minutes; urine, negative; blood culture, negative.

The clinical diagnosis was left tuboovarian abscess with pelvic peritonitis.

Treatment consisted of forced fluids, Fowler's position, and sulfathiazole. The patient was typed for the first of a number of small blood transfusions and found to be Group 0 (Landsteiner), Group 4 (Moss), or Group 1 (Jansky).

\*Presented at a meeting of the New York Academy of Medicine, Section on Obstetrics and Gynecology, November 25, 1941.

The blood selected for the transfusion after a careful cross-matching, was Group 0 from a bank blood three days old. Approximately 450 c.c. had been given when the patient had a mild chill that was easily controlled by heat. She was given 250 c.c. of 1½ per cent sodium bicarbonate. The following morning she was desperately ill with a generalized peritonitis and marked icterus. The pelvic mass previously noted could not be felt. The urine showed the presence of bile with urobilogen positive 1 to 40. The benzidine test was negative. Microscopically, no red or white cells were found. The icterus index was 125 mg. per cent. Urea nitrogen was 9.8 mg. per cent. There was no urinary suppression. Cholesterol was 101 mg. per cent. Cholesterol esters were 38 mg. per cent.

Clinically, it was felt that the pelvic mass had ruptured, either due to the vaginal examination or spontaneously and had caused a generalized peritonitis. The jaundice was ascribed to the use of bank blood, or to the sulfathiazole.

During the next twelve days the icterus gradually cleared up. The white blood count remained high, but there was a drop of the red blood count to 2,940,000 and hemoglobin to 50 per cent. The pelvic infection localized and pointed suprapubically. A celiotomy was performed under local anesthesia and a large amount of pus was evacuated from a pelvic abscess.

Due to the poor condition of the patient a second transfusion was considered imperative. This time warm fresh citrated blood was used in order to avoid another reaction. Four hundred and fifty cubic centimeters of blood were introduced, when once again the patient developed a chill followed by a rise in temperature to 106° F. The urine contained bile and urobilogen in dilution of 1 to 20. No hemoglobinuria was noted, but there was some urinary suppression. The urea nitrogen was 37 mg. per cent. A generalized icterus was present. The heterophile antibody reaction was negative and the cell fragility test was well within normal limits.

Because of the two transfusion reactions, it was felt that some unrecognized incompatibility existed which required further investigation. A study by Wiener and Forer, since reported,<sup>1</sup> showed the patient's blood to be Group 0, Type N, Rh negative and to contain two distinct irregular isoagglutinins, namely, anti-Rh and anti-M, which reacted with the donor's blood and caused the severe reactions noted above. Auto-agglutination was ruled out by the absence of agglutination in mixtures of the patient's cells and serum. Accordingly Group 0 donors were sought who belonged to Type N and were Rh negative. Not until 28 donors had been tested was the proper donor obtained. The donor selected was Group 0, Type N, Rh negative, and 500 c.c. of his blood were given without any reaction. Two weeks later another transfusion, from the same donor, was given without incident. The patient subsequently received three transfusions without reaction from two donors selected by Dr. Wiener.

During the following two months, the resistance of the patient was increased by the aid of transfusions and general supportive therapy. On two occasions the pelvic abscesses re-formed and were drained by posterior colpotomies. Subsequently a laparotomy was performed and a



tuboovarian abscess on the left side removed. The patient made an uneventful recovery. Follow-up examination revealed the patient in good health.

## COMMENT

In 1940 Landsteiner and Wiener<sup>2</sup> reported the presence of an agglutinin which was developed in the sera of rabbits by the injection of blood from the *Macacus rhesus* monkey. The sera when tested with human blood showed the presence of a new agglutinable substance in the red blood cells. They called this the Rh or rhesus factor. Since then it has been found that 85 per cent of human beings of the white race have the Rh factor, and are called Rh positive. The remaining 15 per cent who do not have this factor are referred to as Rh negative.<sup>3, 4</sup>

The role of the Rh factor as the cause of blood transfusion reactions may be explained as follows: An Rh negative mother bears a fetus that has inherited the Rh antigen from an Rh positive father. The factor is inherited as a dominant property.<sup>4</sup> The antigen of the fetus diffuses through the placental barrier and stimulates the formation of anti-Rh agglutinins in the mother's blood.

Should the mother require a transfusion and a Rh positive donor is used, agglutination and hemolysis of the transfused blood will occur due to the presence of the anti-Rh agglutinins.

This explanation does not explain all blood transfusion reactions, but it is a likely answer to reactions that occur in women who are Rh negative and have borne Rh positive children. The presence of anti-Rh agglutinins may be readily determined by the method of cross-matching recommended by Levine.<sup>5</sup> The mixture of patient's serum and donor's cells is incubated for thirty minutes at 37° C. and then centrifuged at low speed (500 r.p.m.) for one minute. The anti-Rh agglutinin usually reacts better at 37° C. than at room temperature. The simplicity of the procedure warrants its use before giving a transfusion to any woman who has been pregnant, or who has previously received a blood transfusion. If a woman has never been pregnant but for some reason received a transfusion from a Rh positive donor, enough anti-Rh agglutinins may be formed as to cause a transfusion reaction at a subsequent time if the same or any other Rh positive donor is used again.

## SUMMARY

A case is presented in which a patient suffered two severe blood transfusion reactions, due to anti-Rh isoagglutinins. By selecting donors of the same group who were Rh negative, five transfusions were given without incident.

I wish to express my thanks to Dr. A. Tamis and Miss Helen Samlowitz for their aid in the composition of this paper.

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## IMMEDIATE POST-PARTUM REPAIR OF OLD PERINEAL LACERATIONS

### A SURVEY OF PERSONAL EXPERIENCES WITH NOTES ON INDICATIONS AND LIMITATIONS OF THE PROCEDURE

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THE perineal structures are the most abused in the birth tract during parturition. This is true in normal births as well as with instrumental procedures, although perineotomy lessens residual trauma. In addition, the perineum often matches the abdominal wall in the inadequacy of post-partum involutional change. One may therefore expect to find in most multiparous patients, perineums which are (1) torn to varying degree, with or without associated rectocele and less frequently cystocele, or (2) generally relaxed from involutional failure after parturitional overdilatation. Post-partum examinations made by any observant physician confirm the frequency of these findings. Even "normal spontaneous delivery" of a small fetus is followed on occasion by pelvic relaxation totally disproportionate to the probable trauma.

Consequently, when the past history of the pregnant woman indicates previous damage, either by character of labor, size of fetus, instrumental intervention, or puerperal morbidity, one looks for and commonly finds residual parturitional trauma of varying degree.

The question posed for the physician now is this, "Is it safe, feasible and recommendable to repair old pelvic lacerations of varying degree immediately following subsequent childbirth?"

It has been customary over many years for one of us (E. G. W.), assuming the answer of the question to be "yes," to repair such old lacerations and relaxations immediately post partum.

To assess more rationally the validity of such an assumption, we have carefully followed a group of patients upon whom reparative operations were performed during the past five years (Table I).

#### CLASSIFICATION OF CASES

In an analysis such as this, an astute reader may question the sorting of cases. Accordingly it is expedient to indicate clearly our position regarding the method of allocation. We regard as second-degree perineal

lacerations all those involving the perineal body which result in partial or complete separation of the musculofascial structures from the bulbocavernosus muscles to the sphincter ani. The divulsion of the bulbocavernosus (constrictor cunni) muscles permits a "marital gaping" of the introitus which becomes progressively more patent, as the rent involves more of the structures in the urogenital diaphragm. With practically all such lacerations there is a rectocele evincing perirectal fascial damage of some degree. The posterior vaginal support is weakened and the "rectocele" ranges from a mucosal overhang to a gross fascial defect with complete herniation of the anterior rectal wall. Since it is a not unreasonable assumption that the causative instrumentality (heredity, progeny or steel) will permit of damage to lower vaginal tissues as easily as perineal, the end result of rectal wall damage depends upon other factors. These are the extent of the initial lesion, competence of the repair immediately effected, the adequacy of involution, and the post-partum state of activity. Inasmuch as the corrective procedures (and likewise the operative hazards) for the different types of posterior

TABLE I. IMMEDIATE POST-PARTUM REPAIR OF OLD PERINEAL LACERATIONS

		NUM- BER	MOR- BID	IMMEDIATE RESULTS		LATE FOLLOW- UP			P.O. DYSPA- REUNIA
				PRI- MARY UNION	IN- FECTED	4 WK.	3 MO.	RESULT GOOD	
GROUP I	1. 2° Perineal lac- eration and rectocele	75	4	73	2	69	71	67	4
	2. 3° Perineal lac- eration	6	2	5	1	6	6	5	1
	Total	81							
GROUP II	1. 2° Perineal lac- eration and rectocele	43	3	42	1	42	39	36	3
	2. 3° Perineal lac- eration	2	1	2		2	2	1	1
	Total	45							
GROUP III	1. 2° Perineal lac- eration and rectocele	20	2	19	1	20	19	14	5
	2. 3° Perineal lac- eration	2	1	2	0	2	2	2	
	Total	22							
	Grand Total	148	13	143	5	141	139	125	14

vaginal wall relaxation are essentially the same, in this study all were grouped with the second-degree perineal lacerations. Third-degree perineal lacerations here include all complete disruptions of the perineum, involving the sphincter ani and combined with various degrees of fecal incontinence. In several instances the partially healed rent involved the anterior rectal wall.

Not shown in the table are 9 cases of cystocele repaired immediately after childbirth. While not properly encompassed in this presentation, they are recorded here to allow of pertinent comment later.

#### TYPE OF REPAIR

It would be reckless to say that repair technique is standardized, since each operation and more especially each operator is individualized. Basically, all good perineal operations are alike. They consist in resection and reposition of lacerated and divided tissues and resection or reduplication of overstretched and attenuated structures. This means resuturing the levator ani muscles, re-forming the rectovaginal septum, and restoring the structures of the urogenital diaphragm. With third-degree lacerations, clear identification and resuture of the torn sphincter ends is the all-important additional requirement to those cited. All operations in this study were designed to effect such ends. Chromic catgut No. 0 or No. 00 was used throughout, except for No. 1 in the levator ani and sphincter ani. In two third-degree repairs, silver wire was used through the sphincter ani, with no greater satisfaction or convincing evidence of indispensability.

The use of fine catgut and a minimum of buried knots unquestionably results in greater ease for the patient, less tissue reaction and infection, and sounder healing. Yet, the repair is more difficult at this time than in the nonparturient. The field is obscured by blood from the uterus and highly vascularized tissues. Large varices are more commonly encountered. Hemostasis, more difficult, assumes excessive importance in anemic, debilitated, or profusely bleeding patients. The tissues are easily recognizable by those thoroughly familiar with the field, but the sutures must be carefully placed, with proper tension, in the succulent structures.

#### ANALYSIS OF DATA

Except for Group I, in which local anesthesia was used in about 20 per cent of the cases, spinal anesthesia was most commonly utilized. Dissolved in 3 c.c. of spinal fluid, 50 mg. of novocain crystals in the fourth lumbar space was the usual amount. Gas-ether was used in approximately 30 per cent of the entire group.

Thirteen, or 9 per cent, of the entire number were morbid. Not all morbidity was ascribable to the operation performed. Little hazard seemed to be added to the parturition just experienced, since only 5 became locally infected, and there were only 3 complete breakdowns. There were no deaths.

Our post-partum care consists mainly in cleanliness. Intravaginal antisepsis is rarely resorted to but neither is it derided. It is our belief that from a bacteriologic standpoint the vaginal structures have not forgotten that they were once part of a cloaca, and are ordinarily re-

sistant to fecal contamination. The bowels therefore are not "tied up," but normal movements encouraged and low enemas used. Catheterization is dispensed with unless bladder atony appears or pyelocystitis is present.

Analgesics for pain are not commonly needed. Moist heat in the form of witch hazel or saline applications or flaxseed poultices is generally better received than dry heat. Short wave therapy brings pain relief and subsidence of congestion in nonsuppurative perineal inflammation. It is regularly used when there is actual or suspected endometritis.

On follow-up examination, 141 patients were seen in four weeks, and 139 three months post partum. The result was recorded as "good" in 125 of the 148 operations done. This means the patient was relieved of any symptoms reasonably ascribable to the old perineal damage, and had an anatomically restored lower vaginal tract. She was also free of any symptoms reasonably chargeable to the operative procedure itself. Fourteen patients complained of dyspareunia. In all cases the introitus was too tight and in 6 cases it was of the "dashboard" type. A number of patients had vaginal constriction but no marital complaints, and subsequent physiologic dilation may be assumed. Irrespective of accuracy of anatomic repair, dyspareunia is considered a highly objectionable complication and largely avoidable. It is likely to follow if there is excessive removal of redundant vaginal musculo-fascial tissues, if the levators are too broadly "blocked" together, or if a high "dashboard" perineum is built up at the expense of an adequate vaginal orifice. The surgeon must remember the physiologic assistance of involutional change in the post-partum vagina, in estimating the degree of operative constriction of the vagina and the introitus. Overzealous reduction of orificial and vaginal capacity is the leading cause of subsequent dyspareunia.

The 9 cystocele repairs done immediately post partum were of unusual interest because of the difficulties experienced. It was found that patients cannot be positioned properly; the flaccid, edematous cervix tears easily and bleeds freely with traction; and it is difficult to keep the field clear. The dissection itself in the highly vascular field is bloody, and the tissues friable and not clearly recognizable. Shortening of the anterior vaginal wall was noted in one case and the cystocele repair was deficient in two others. In the other six, the operating technique was less flattering to the surgeon's ego than the results as observed some months later. These were noted to have been satisfactory.

#### SUMMARY

1. Immediate post-partum repair of old perineal lacerations is a safe and feasible gynecologic procedure.



2. Reparative operation is especially recommended for a symptom-producing condition in a patient fearing or unable to afford rehospitalization at a more propitious time.

3. Although later operation is cleaner and less bloody, and allows a better technique, there is little added risk from immediate operation, and the morbidity incidence is low.

4. Perineal infection was noted in 5 of 148 reparative operations, and the repair broke down completely in three of these.

5. The outstanding postoperative complication is dyspareunia and this is avoidable.

6. Immediate post-partum repair of cystocele is much less satisfactory and offers reasonable probability of effective correction only in selected cases and in expert hands. It is not without danger and more satisfactory results are generally obtained by later operation.

### RUPTURED OVARIAN PREGNANCY

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IN THE eighteen years, from October 1, 1923, to October 1, 1941, a total of 24,733 pregnant patients were treated at the New England Hospital for Women and Children. These cases were classified as follows:

	NUMBER	PER CENT
Delivered (term and premature)	23,133	93.53
Miscarriages	1,494	6.04
Ectopic pregnancies	106	0.43
Total pregnancies	24,733	100.00

However, of all the extrauterine pregnancies recorded at this hospital, the case to be reported in detail below is the only ovarian pregnancy found. The incidence in proportion to the total number of ectopic pregnancies is 0.94 per cent, and the rate of occurrence in relation to the total number of pregnancies is 1 in 25,000.

This case of ovarian pregnancy presents all of the classical features required for the definitive postoperative diagnosis of such cases, as enumerated by Spiegelberg.

A review of the literature of the past ten years shows a great increase in interest in the subject of ovarian pregnancy. In 1932, Wollner<sup>1</sup> published a case of ovarian pregnancy and offered some interesting comments on its etiology. In addition, he carefully scrutinized the previously reported cases and found that only 48 of the 87 cases were acceptable as primary ovarian pregnancies. Gandy<sup>2</sup> and Hyams<sup>3</sup> also reported cases and offered suggestions as to the etiologic factors. Though we accept these explanations, it has been suggested that perhaps many of the reported cases may actually represent tubal pregnancy with complete abortion,<sup>4</sup> an idea not generally accepted.

Miller and Heimark<sup>5</sup> have commented on the discrepancy between the figures of various authors on the frequency and incidence of this condition. It is felt that the literature is incomplete and confusing and only by the successive reports will the true incidence be discovered. Young and Hawk<sup>6</sup> reported cases of ovarian pregnancy with an incidence of 0.7 per cent of all uterine pregnancies in their series of 148 cases. Jordan and others<sup>7</sup> mention Strezoff who found only one secondary or superficial case in 350 extrauterine pregnancies, and Zimmerman who had two cases out of 120 ectopic pregnancies, with only one acceptable as primary intrafollicular pregnancy. In Cosgrove's experience, only one uncertain primary ovarian pregnancy is mentioned, but Randall and Wellbrock<sup>9</sup> report a case and state that the incidence at the Mayo Clinic is 2 of 400 ectopic pregnancies.

Jordan and others<sup>7</sup> have presented one of the most complete histologic descriptions of this type of case. They mention the histologic development of such an entity and differentiate between primary and secondary ovarian pregnancy. They speak of intrafollicular and extrafollicular or superficial ovarian pregnancy types.

Numerous other case reports by various authors<sup>10-12, 16-22, 23-33</sup> bring the total of cases reported in the American and English literature to 40. If we add Wollner's 48 cases, and the one to be discussed below, we thus have a total of 89 cases of this rather rare condition, thus forming a good nucleus for further study of this most interesting pathologic entity.

#### CASE REPORT

This 26-year-old white patient, married for seven years, was first seen at the office on Sept. 30, 1941, with a complaint of staining for the previous three weeks. She had begun to menstruate at eleven, and her periods always occurred every twenty-six to twenty-eight days. She would flow for five days with moderate dysmenorrhea on the first and second days. Her last normal period started on July 28, 1941.

On Aug. 15, 1941, she experienced an attack of severe abdominal pain. The physician who examined her felt that she had a "bowel disturbance," and advised the administration of a soapsuds enema. Five days later, on August 20, a brown vaginal discharge appeared which persisted for two weeks. Then she had an episode of profuse dark red bleeding which continued for two days, on September 3 and 4. The bleeding and staining then stopped for two weeks until September 19, when they recurred. This staining persisted until the time she presented herself for examination. During the previous month, the patient had experienced no digestive disturbance except nausea, and the only urinary symptom was frequency.

The family history and social history were noncontributory. The past history revealed the fact that an appendectomy was performed eleven years before without any postoperative complications. Two years ago the patient had had a right breast tumor removed, which was diagnosed as a lipoma. Since the patient was desirous of becoming pregnant, a hysterosalpingography was performed two years ago and the patient was informed that she could not become pregnant. There was no history of any serious medical illnesses. The gastrointestinal history revealed that the appetite was good but the bowels were slightly constipated. There was no history of vomiting or of bloody or tarry stools. Jaundice and postprandial discomfort were absent. There had been

episodes during the past few years of pain in the left lower quadrant on walking and working, but this persisted only one day at a time. The genitourinary history contributed the fact that dysuria, lasting one week, occurred five years ago, with a probable diagnosis of pyelitis, and recurred one month ago. There was no history of gonorrheal infection. The cardiorespiratory systems were essentially normal.

The physical examination revealed a well-developed, but pale and thin, female in an apprehensive state. Pupils were equal and reacted to light and accommodation. Breasts had a slightly pigmented areola, but no masses or tenderness, and a healed scar on the right breast. Blood pressure was 100/68. The abdomen revealed generalized tenderness, especially in the left lower quadrant. There was a palpable mass over the region of the right adnexa which was the size of an egg. Spasm and rebound tenderness were elicited in both lower quadrants. There was a healed right rectus incision. The liver, spleen, and kidneys were not palpable. The reflexes were bilaterally hyperactive, and the extremities were normal.

Pelvic examination revealed a marital outlet and no posterior or anterior relaxation. No vulvovaginal or urethral infection were noted. The cervix was soft and presented some suggestion of cyanosis. The uterus was somewhat enlarged and soft, with no irregularities to suggest myoma, but displaced slightly to the right. In the right adnexa was a mass about the size of an egg and somewhat tender. In the left adnexa, another mass, about the same size as that on the right, was present and distinctly tender. There was some pain on moving the cervix to the right. Because she did not wish to go to the hospital for further study, she was allowed to go home, remaining under constant care of a nurse. A Friedman test was done the following morning, but the rabbit died immediately. Another test repeated the following morning killed a second rabbit, and a third done the next morning with small doses of urine was reported as positive.

Until October 9 the patient remained fairly comfortable with occasional slight staining. On this day she was suddenly seized with a severe, sharp, agonizing pain in the left lower quadrant. There was no associated nausea or vomiting. Abdominal examination revealed the presence of a definite mass in the right lower quadrant. The vaginal examination had not changed except that tenderness was greater and was most marked over the palpable abdominal mass. The abdominal mass in the left lower quadrant was the same size. Hospitalization was immediately advised.

*Laboratory Studies.*—Blood specimen on admission revealed a hemoglobin content of 12 Gm. by the Sahli standard; red blood count, 4.51; white blood count, 7,650, with a differential count of 61 polymorphonuclears, 26 lymphocytes, 6 monocytes, 5 basophiles, and 2 eosinophiles. The urine was yellow, cloudy, and acid with a specific gravity of 1.006 with no albumin or sugar. A centrifuged sediment contained 1 to 3 white blood cells per high power field and some large epithelial cells.

The preoperative diagnosis was ectopic pregnancy on the left and twisted ovarian cyst on the right.

*Operative Procedure.*—Under spinal anesthesia, a midline suprapubic incision was made. On opening the peritoneal cavity 50 c.c. of free blood was found with considerable clotted blood. The omentum was

adherent to the parietal pelvic peritoneum. When this was dissected free, the pelvic organs were exposed. The uterus was slightly enlarged and not discolored. The left ovary was normal except for a thin-walled solitary cyst containing dark-colored fluid. On inspection the right ovary proved to be the seat of pathology. It was approximately 3 by 3 by 2 inches in size, and at its upper pole there was a ragged tear about one inch long, from which there was a constant ooze of blood. This tear communicated with a cavity that was filled with a blood clot. The possibility of an ovarian pregnancy was considered and the ovary inspected again. It was found to have its normal attachments and relations and to be entirely free of its tube. Both tubes were carefully inspected, and no sign of any pathologic change could be seen or palpated. The entire right ovary was removed and its pedicle was doubly ligated. The cyst of the left ovary was resected and the bleeding was controlled with fine ligatures. The peritoneal cavity was carefully cleaned of blood and clots, and the abdominal wall was closed in layers without drainage.

The patient made an uneventful convalescence and was discharged on the fourteenth postoperative day.

*Discharge Diagnosis.*—Ruptured right ovarian pregnancy and solitary cyst of left ovary.

The report of Dr. G. Lindh Muller, the hospital pathologist, was as follows:

*Pathologic Examination.*—(No. P-41-1325.) Specimen consisted of the right ovary and a portion of the left ovary. The right ovary was an irregular mass, 7.5 by 7 by 4.5 cm. in size, with a ragged tear at one pole. The surface of the intact portion was reddish in color and slightly nodular. In one area a few small translucent cysts were seen. The interior of the cystlike mass was filled with large amounts of dark-clotted blood. Cut sections of the wall revealed a rim of recognizable ovarian tissue which contained hemorrhagic areas and a few small cysts filled with clear fluid. Grossly there was no evidence of placental tissue and no embryo was seen.

*Microscopic Examination.*—Sections from the periphery of the mass showed ovarian stroma with a developing follicle and small atresic follicles. Several corpora albicantia were present. Adherent to this shell of ovarian tissue was a partly degenerated blood clot with some fibrinous strands. It contained shadow-like degenerated chorionic villi. In several sections well-preserved chorionic villi and small areas of decidual cells were present. Such a section is illustrated in Fig. 1, which shows the cortex of the ovary with a developing follicle and several corpora albicantia. In the lower right portion of the section is the partly degenerated blood clot separated from the ovarian tissue by a layer of hyaline material. Fig. 2 is a magnification of the blocked area in Fig. 1. On the right center edge is a well-preserved chorionic villus without any recognizable vessels but surrounded by a thin layer of syncytium and with a collection of syncytial cells on one side. At the extreme left, opposite this villus, many decidual cells are seen in the wall at the site of implantation. There was no endometrial tissue in the sections examined.

Specimen from the left ovary consisted of a cyst membrane which microscopically revealed a cystic corpus luteum.

*Pathologic Diagnosis.*—Ruptured ectopic pregnancy, primary in the right ovary, and corpus luteum cyst of the left ovary.





Fig. 1.—Cortex of the right ovary, showing site of implantation of the ovum and blood clot.  $\times 60$ .

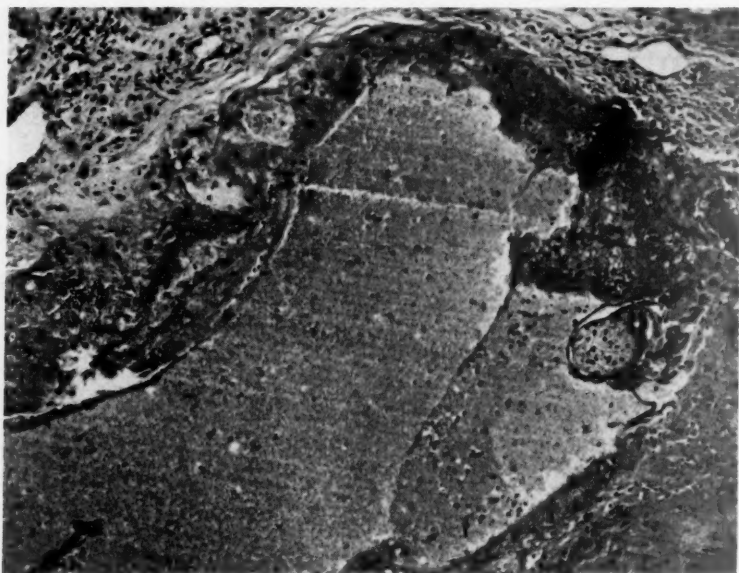


Fig. 2.—Magnification of blocked area in Fig. 1, with a villus and decidua.  $\times 160$ .

#### SUMMARY

A case of ovarian pregnancy in a young woman of 26 years, with a description of the pathologic specimens, is reported in detail, and the literature to date is discussed.



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**Cruickshank, Robert: Bacteriology of Impetigo Contagiosa, Lancet 2: 275, 1941.**

A bacteriologic study of 23 adult cases of impetigo revealed hemolytic streptococci of Lancefield Group A in 15 cases. In most instances the streptococcus was the predominant organism. Five of the 15 showed hemolytic streptococci in throat cultures. *Staphylococcus aureus* was found in 18 of the 23 skin lesions and was present in the 8 cases that failed to yield hemolytic streptococci. The staphylococcus was regarded, rightly or wrongly, as a secondary invader.

The author also points out that in Denmark an epidemic curve for impetigo with its peak in late autumn has been described. In England a minimal incidence is described in summer followed by a rapid rise in early autumn with the peak in November, a slight drop in December, and another rise to a maximum in January. This curve parallels but antedates by three to four weeks the incidence curve of scarlet fever.

CARL P. HUBER.

## UNUSUAL COEXISTENCE OF GRANULOSA CELL TUMOR AND OVARIAN TERATOMA CONTAINING THYROID TISSUE\*

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IN GENERAL, 80 per cent of ovarian tumors are cystic and 20 per cent are solid (Dockerty). Dermoid cysts constitute about 10 per cent of the cystic tumors and are usually unilateral. The incidence of thyroid tissue found in dermoid cysts of the ovary varies from 1.5 per cent to 28.5 per cent, as cited by Wynne and his associates, quoting various authors. Probably a midground of about 10 per cent would be more correct. They also noted that the first strumal tumor of the ovary (ovarian tumor of thyroid tissue) was described by Gottschalk in 1899 under the name of "folliculoma malignum ovarii." According to the same authors a tumor of similar structure was recognized as containing thyroid tissue by Pick in 1902. Strumal tumors are most common among women more than forty years of age, may be cystic or solid, and usually cause symptoms referable to mechanical influence alone. Witherspoon stated that of the 50 recorded cases reviewed by him, in only 11 was the tumor composed entirely of thyroid tissue and in only two of these was it associated with goiter. Kovács observed the subsidence of definite symptoms of exophthalmic goiter after removal of a strumal tumor of the ovary. Trapl suggested that strumal tumors of the ovary may function vicariously as thyroid. Masson and Mueller reported 6 cases of ovarian tumors of thyroid tissue, in 3 of which they determined the iodine content. They found the iodine content in their Cases 1, 3, and 4 to be 0.105, 0.031, and 0.011 per cent dry weight, respectively. These authors stated that Ordtmann estimated the iodine content of the thyroid gland at approximately 0.1 per cent.

Of the solid ovarian tumors, the granulosa cell type constitutes 10 per cent. According to Te Linde, these tumors are responsible for about 1.1 per cent of postmenopausal bleeding. It is important to note that bleeding caused by this tumor is periodic and may be clinically indistinguishable from menstruation (Novak). This adds much weight to the thesis that periodic bleeding can occur in the absence of ovulation, for the stimulus afforded by the cells of the granulosa cell tumor is not associated with ovulation. Of other conditions causing postmenopausal bleeding, malignant lesions are responsible for about 60 per cent and benign lesions for about 40 per cent. The most common cause of postmenopausal bleeding is carcinoma of the cervix (37 per cent) with carcinoma of the fundus second (15 per cent). Prolapse with ulceration of the cervix accounts for 11 per cent, cervical polyp for 6 per cent, and endometrial polyp for 4 per cent. No other single condition accounts for more than 5 per cent of the remainder, according to the figures of Te Linde, in a survey of 179 cases of postmenopausal bleeding.

\*Submitted for publication, February 10, 1942.

## REPORT OF A CASE

A 56-year-old obese white woman first entered the Mayo Clinic on Aug. 4, 1926, for "an examination of her pelvis." Past medical history had been essentially negative. She had one child; there had been no other pregnancies. For sixteen years the patient had been experiencing symptoms of the menopause; her last menstrual period had occurred early in 1925. Eight years prior to admission she had experienced a severe episode of vaginal bleeding. The bleeding had ceased following "clipping" from the uterus of some tissue which, she had been assured, was not malignant.

Examination here on Aug. 4, 1926, disclosed a cervical polyp; the uterus was enlarged two times normal size and the enlargement seemed to be more on the right side than on the left. The clinical diagnosis was cervical polyp and fibroid of the uterus or an ovarian cyst (the former more probable). Immediate operation was not insisted on but the patient was advised to have an examination every six months and to return for an operation if the mass gave trouble or increased in size.

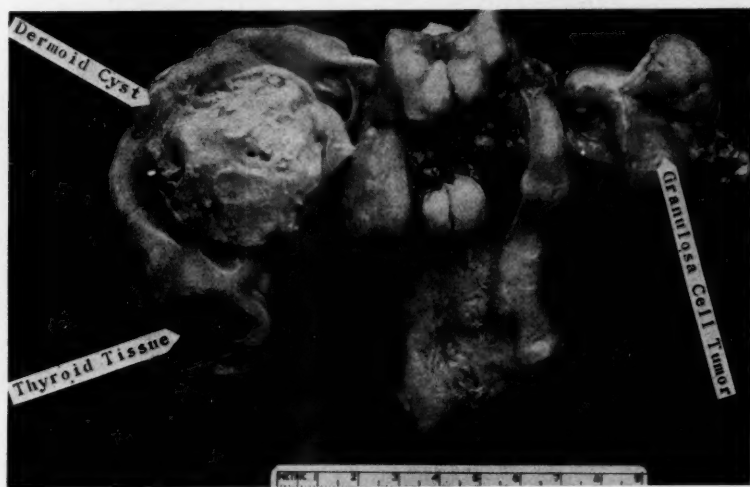


Fig. 1.—The uterus is large for a senile organ. The other features are indicated by the arrows.

The patient returned to the clinic on Nov. 6, 1941. She stated that she had been well until July 17, 1941, at which time she had slight vaginal bleeding. Curettage was performed at that time with removal of a benign polyp. There was no further bleeding until Aug. 28, 1941, at which time, the patient said, she had experienced a profuse "period." Another curettage was performed and multiple benign polyps were found and removed. The physician also told her she had a tumor of the right ovary. Since this last operation, the patient had been suffering from a brownish watery discharge gradually diminishing in amount.

At examination on November 6, the patient appeared unusually well preserved for her age (looked ten to fifteen years younger). Her weight was 175 pounds (79 kg.), blood pressure 175 mm. of mercury systolic

and 90 diastolic, and pulse 84. Results of examination of the heart, lungs and abdomen were negative. Pelvic examination revealed a tumor the size of a grapefruit filling the right side of the pelvis and apparently attached to the uterus. The diagnosis was ovarian cyst (right) or a degenerating fibroid.

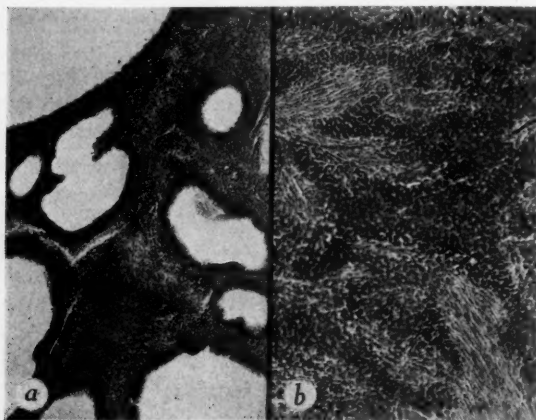


Fig. 2.—*a*, Cystic glandular hyperplasia of endometrium with some evidence of differentiation as shown by coiling of the glands (hematoxylin and eosin  $\times 50$ ); *b*, granulosa cell tumor, cylindroid pattern, with transition to spindle-shaped theca cells. These theca cells contained lipoid as demonstrated by appropriate stains (hematoxylin and eosin  $\times 125$ ).

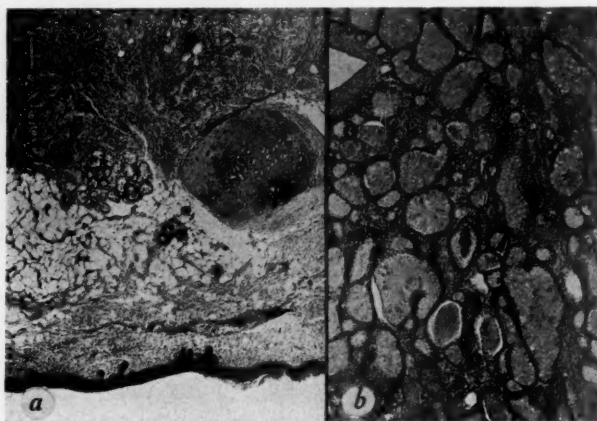


Fig. 3.—*a*, Dermoid (cystic teratoma); note skin, sweat glands, smooth muscle, adipose connective tissue and cartilage (hematoxylin and eosin  $\times 30$ ); *b*, the nodule of thyroid tissue. Most of the vesicles are well filled with colloid (hematoxylin and eosin  $\times 55$ ).

At operation on Nov. 8, 1941, a right ovarian cyst was found in addition to several small uterine fibroids. The uterus was slightly enlarged. Hysterectomy with bilateral salpingo-oophorectomy was performed.

**Pathologic Report.**—The specimen consisted of uterus, tubes, and ovaries. The uterus weighed 70 Gm. (normal weight 40 Gm.). The left ovary measured 2.5 by 2 by 2 cm. and was solid in consistency. Surfaces made by cutting were homogeneously grayish brown and somewhat fibrous. The right ovary measured 11 by 10 by 6 cm., weighed 455 Gm.,

and was cystic. On section the cyst was seen to be filled with semisolid gelatinous, greasy material containing hair. In the wall was a semisolid translucent brownish nodule, 2.5 cm. in diameter, which on cut section grossly resembled normal thyroid. The uterus was large and contained numerous fibromyomas, ranging from 5 mm. to 2 cm. in diameter. The endometrium was 5 mm. in thickness and presented numerous polyps. The cervix was fibrotic and contained a few small cysts filled with gelatinous material. The Fallopian tubes presented chronic inflammatory changes (Fig. 1).

*Microscopic Examination.*—Multiple leiomyomas of the uterus, cystic hyperplasia of endometrium (Fig. 2, *a*) with polyps (benign), chronic cervicitis, bilateral chronic salpingitis, granulosa cell tumor of the left ovary showing transition to theca cell type (Fig. 2, *b*) (Dockerty), and dermoid cyst (benign teratoma) (Fig. 3, *a*) of the right ovary containing thyroid tissue were observed (Fig. 3, *b*). The latter showed Grade 2 (on basis of 1 to 4) parenchymatous hypertrophy (Fig. 4).

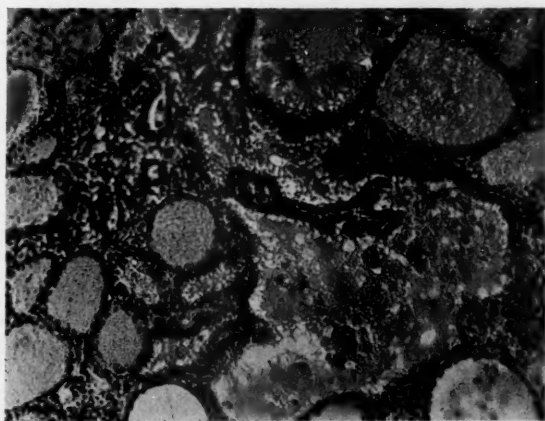


Fig. 4.—The region of "ovarian exophthalmic goiter." Note the tall epithelium, papillary infoldings and thin vacuolated colloid (hematoxylin and eosin  $\times 165$ ).

This case, in retrospect, illustrates the importance of suspecting granulosa cell tumor when any patient past the menopause presents herself because of periodic vaginal bleeding and especially when curettage from such a patient reveals endometrial hyperplasia. It also emphasizes the difficulty of distinguishing, clinically, uterine fibromyomas from ovarian cysts. Finally, from a purely pathologic viewpoint, the extremely rare coexistence of granulosa cell tumor and hyperplastic strumal tumor is of unusual interest. Search of the literature revealed only one other similar instance (Frankl).

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## BILATERAL BRENNER TUMOR OF THE OVARY

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**A**LTHOUGH Brenner tumors are comparatively rare, still they are probably not as infrequent as the literature would have us believe. Up to 1938 Varangot<sup>1</sup> was able to collect 108 cases from the literature. Since that time several additional cases have been recorded; 1 by Eleizegui,<sup>2</sup> 10 by Docherty and MacCarty,<sup>3</sup> 2 by Walton,<sup>4</sup> 14 by Novak and Jones,<sup>5</sup> 10 by Smith and Pettit,<sup>6</sup> 9 by Timmerberg,<sup>7</sup> 1 by Lemgruber, MacClure and de Oliveira,<sup>8</sup> 1 by Chiray, Albot and Balmez,<sup>9</sup> 1 by Siegel<sup>10</sup> and 1 by Etcheverry and Martinez de Hoz<sup>11</sup> bringing the total to 159 (including this case). We feel that this case should be presented because of the unusual clinical history, the gross appearance of the specimen and because of the fact that we will be able to arrive at a true estimate of the incidence of these tumors only if all cases are reported.

In 1899 Orthman<sup>12</sup> described what we now consider the first case of Brenner tumor, followed in 1907 by Brenner's<sup>13</sup> three cases to which he gave the name "oophoroma folliculare," because he believed the source to be the follicle. However, since Meyer's<sup>14</sup> paper and explanation of their origin from Walthard<sup>15</sup> inclusions, these tumors have been more accurately classified and their histogenesis has been more clearly defined. Schiller<sup>16</sup> points out that in some instances these tumors may arise from Wolffian epoophoron tubules which are included in the ovarian hilum and which may form epithelium like that normally found in the urinary tract. However, most investigators favor the Walthard inclusion source.

The Brenner tumor is slow growing and considered a benign lesion. It is usually unilateral, although it may be bilateral. Over 50 per cent occur beyond the age of fifty years. It produces no hormonal disturbances of the endometrium and no characteristic symptoms so that it is usually found incidentally at operation or autopsy. The size varies between a few millimeters to several centimeters, the largest recorded being 15 pounds as reported by Neiman.<sup>17</sup> The tumor may assume a solid or cystic form. The former has much the appearance of a fibroma, the cut surface, however, presenting a yellowish tint. Necrosis and hemorrhage are rare findings. Two features are necessary for the microscopic diagnosis, namely the characteristic nests of epithelial cells, which resemble squamous cells, although they do not possess intercellular bridges or keratin and a fibrous connective tissue stroma surrounding the epithelial nests.

### CASE REPORT

L. M., a white female, married, age 50 years, was admitted to Temple University Hospital on April 1, 1941. Her chief complaints were stiff-

ness and swelling of the joints following an attack of "la grippe" in December, 1940.

Systemic inquiry revealed nothing further of significance. Her menses began at an early age and were regular until Dec. 10, 1940. Since then she has had no periods or bleeding and has had no menopausal symptoms.

Physical examination revealed a well-developed and well-nourished adult female. There was enlargement of the isthmus and of the left lobe of the thyroid. Heart and lungs were normal. The abdomen was not tender. The liver and spleen were not palpable, but in the midline

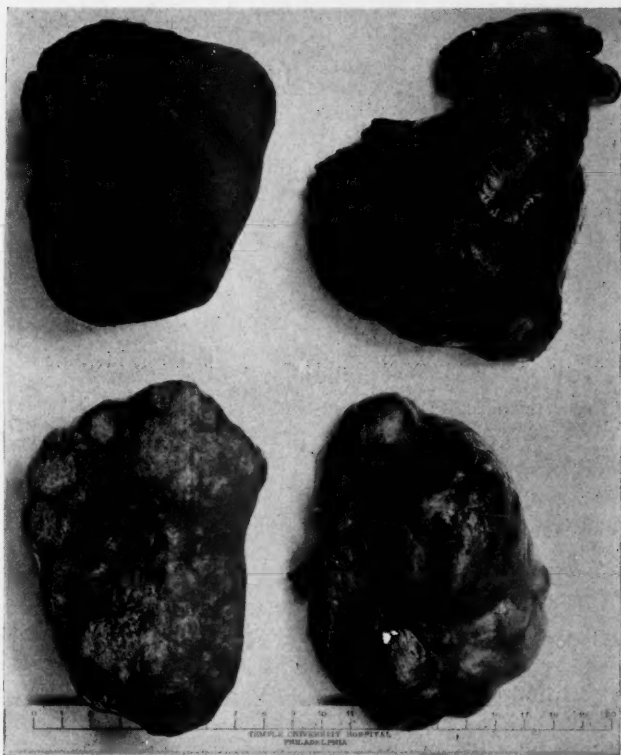


Fig. 1.—Gross specimen of the ovarian tumors. Hemorrhagic necrosis of the right ovarian mass (upper part of photo) is clearly visible.

and slightly toward the right side there was a firm mass which disappeared as it was followed into the pelvis. This apparently represented an enlarged fibroid uterus. The extremities revealed swelling, stiffness, and limitation of the knee and ankle joints with some swelling of both wrists and of the interphalangeal joints of the right middle and index fingers.

On admission, temperature, pulse, and respirations were normal, but on the three following days the temperature rose gradually to 99.8° F. Basal metabolic rate was +30.

Pelvic examination on the day following admission revealed the vulva and vagina to be negative. The cervix was normal except for a profuse

mucopurulent discharge. The uterus was normal in size, retrocessed and fixed a little to the right. A large tender mass was palpated in front of the uterus, occupying the whole of the left pelvis. This was interpreted as a large tuboovarian abscess. Operation was advised and performed on April 4, 1941, with the findings of bilateral ovarian fibromas. The right ovarian fibroma had two twists in its pedicle and was gangrenous. It had almost amputated its pedicle and was in the left pelvis anterior to the broad ligament. The left ovarian mass was free in the abdomen. A bilateral ovariectomy and partial salpingectomy was done and the specimen was sent to the laboratory.

The pathologic report (31129) stated that the specimen consisted of both ovaries and portions of both Fallopian tubes. One tube and ovary (right) was a large reddish black necrotic mass measuring 12 by 7 cm.

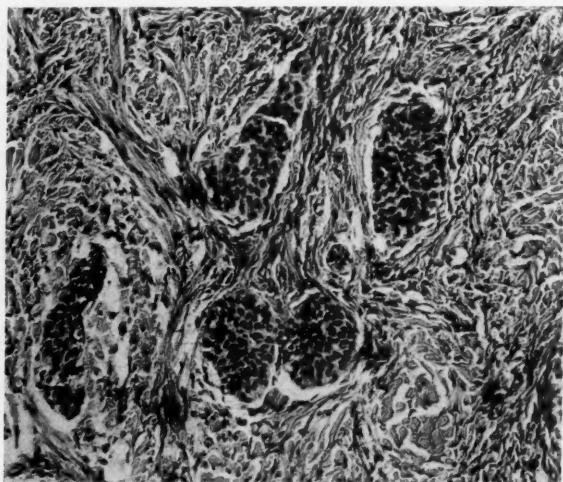


Fig. 2.—Photomicrograph showing the characteristic nests of epithelial cells in a dense fibrous supportive stroma.

Cut sections revealed a trabeculated, reddish black, hemorrhagic, moderately firm parenchyma. In the broad ligament there was a large vascular channel stuffed with blood. The opposite ovary measured 12 by 8 by 7 cm. It was well encapsulated and smooth. The outer surface was lobulated and the cut surfaces presented a white, firm, trabeculated parenchyma, showing scattered areas of softer yellow tissue. The corresponding tube measured 7.5 cm. in length and was grossly normal.

Microscopic sections of the right ovarian mass revealed hemorrhagic necrosis, but in some areas the architecture was well preserved and here were seen nests of epithelial cells embedded in a dense fibrous stroma. The opposite ovary revealed the typical picture of a Brenner tumor showing an occasional area of cyst formation and calcification.

The patient made an uneventful recovery and was discharged on April 21, 1941, much improved with the diagnosis of rheumatoid arthritis, bilateral Brenner tumor, and food allergy.

This case clearly illustrates the apparent silent behavior of a Brenner tumor. Prior to the patient's discharge a curettage of the uterus was done. The fragments, however, were insufficient for a satisfactory histologic diagnosis. They showed only a few glands and a dense stroma.

## SUMMARY

An unusual case of bilateral Brenner tumor in a 50-year-old female is reported. It was complicated by strangulation of the right ovarian mass through torsion of the pedicle.

We are indebted to Dr. H. A. Duncan, Clinical Professor of Gynecology, Temple University Medical School and Hospital, for permission to report this case along with his clinical observations.

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## SARCOMA BOTRYOIDES OF THE CERVIX

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**B**ECAUSE of the rarity of occurrence of mixed mesodermal tumors of the cervix, the following case report is herewith submitted:

S. G. (No. 100,348), aged 45 years, white, Russian Jewess, was admitted to the Beth Moses Hospital on Nov. 23, 1941. This was her fifth admission in a period of thirteen months, at about three- to four-month intervals, and always with the same complaint of irregular vaginal bleeding.

Her menstrual cycle which began at the age of 12, at twenty-eight-day intervals and lasting for six days, had always been of a normal rhythm up to the time of her first admission to the hospital on Oct. 14, 1940. At this time, she had complained of a menometrorrhagia of four months' duration.

Except for the usual diseases of childhood, there was no history of any previous illness. There were no previous operations except for those performed upon her four previous hospital admissions noted above.

She had been married 28 years, and was a gravida viii and para vii, had had one induced abortion and no history of any obstetric difficulties.



All her children were living and well. Both parents were dead of unknown causes. Her husband is at present confined to a mental institution. There is no family history of diabetes, tuberculosis or cancer.

Physical examination revealed a well-nourished female, with a slight tendency to adiposity, who did not appear either acutely or chronically ill. She presented essentially negative objective physical findings except for those noted upon bimanual and vaginal examination. These findings were practically identical with those noted upon her four previous hospital admissions, and consisted essentially of a slightly enlarged uterus, regular in outline, lying in third degree retroversion, and moved forward with great difficulty. The cervix upon inspection again revealed, for the fifth time, the presence of several succulent polyps extruding through the external os. Upon her four previous admissions, she had had a simple polypectomy and uterine curettage; a wide cervical excision, polypectomy, and cauterization upon two occasions; and, upon her last previous admission, a high cervical amputation. Pathologic reports upon all the tissues obtained had signified the presence of benign polyps, although, upon one occasion, the pathologist had expressed a verbal opinion of a suspected malignancy.

The blood pressure was 120/74; urine, negative; Wassermann and Kahn tests, negative. Blood sugar was 80, and urea nitrogen 14. Vaginal, cervical, and urethral smears were negative for gram-negative intracellular diplococci. Blood examination showed hemoglobin 12 Gm.; red blood count, 3,060,000; white blood count, 11,000 with polymorphonuclears 79, eosinophiles 2, and lymphocytes 19.

In view of the patient's age, constantly recurring polyps with bleeding, and a suspected malignancy, it was deemed advisable, at this time, to advocate a total abdominal hysterectomy. Under spinal anesthesia, this was performed on Nov. 28, 1941, with the following findings: The uterus was slightly enlarged, nonadherent and regular except for the presence of a small pedunculated fibroid on its anterior surface. The adnexa were grossly normal. There were no visceral or peritoneal implantations. The cervix was hypertrophied, short, and stumpy, with several grapelike polyps extruding through the external os. There were no glandular enlargements.

*Pathologic Report.*—(Lab. No. 11956—Dr. A. R. Kantrowitz.) *Gross:* Specimen consisted of a completely resected uterus, together with the cervix, measuring 10 by 7 by 5 cm. A pedunculated mass, 1.8 cm. in diameter, was adherent to the anterior wall immediately inferior to the right round ligament. Numerous hemorrhagic polypoid excrescences, ranging up to 0.9 cm. in diameter, projected in grapelike clusters through the external os. The right and left tubes and ovaries were removed together with the uterus. The uterus was opened along the posterior wall. The projecting mass measured 3 cm. in length and up to 1.7 cm. in diameter. It was found to arise from the anterior wall of the cervix. Upon opening into the endometrial cavity, the cavity was found to measure 8.5 cm. in length. The endometrium presented a succulent appearance. When the polypoid mass was raised, the anterior wall was found to present an angry red, finely granular appearance with considerable mucoid secretion, providing a glistening surface. An area of pearly gray thickening was noted on the endometrium at the internal os.



This resulted in a somewhat narrowed endometrial canal. Cross section through the cervix, through the middle of the anterior wall, revealed a pinkish red succulent mass, 1.2 cm. in diameter, deep within the cervical myometrium.

The right and left tubes measured 9 cm. in length, respectively. Their fimbriated ends were patent. The ovaries were of normal size and shape. The right contained an hemorrhagic lateral portion comprising one-third



Fig. 1.—Sarcoma tissue in the cervix (low power).

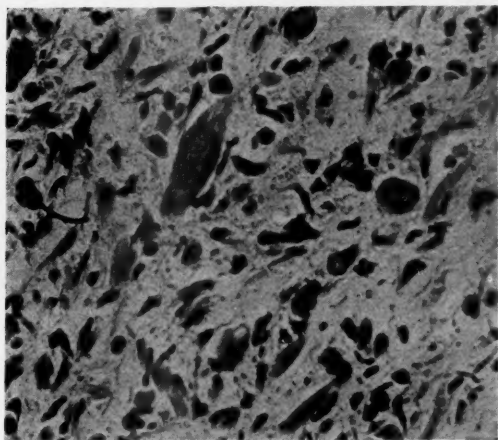


Fig. 2.—Striated muscle fibers in the cervical stroma (high power).

of the ovary. Cross section revealed a small, clot-filled cyst bordered by a golden yellow undulating membrane. The left ovary contained a similar cystic area in its mesial third. This was filled with clear serous fluid.

*Microscopic:* (Figs. 1 and 2.) The endometrium was in a very early secretory phase. Downgrowths of the endometrium were noted in the

myometrium. The cervical polyps consisted of granulation tissue with mononuclear and polynuclear cells. Nests of spindle and round cells were noted within the cervical stroma. In areas the nests presented the appearance of embryonal mesenchyme, with its stellate cells and loose intercellular substance. Considerable atypism and numerous mitoses were noted. In other areas considerable anaplasia was noted. Striated muscle fibers were also present.

*Diagnosis.*—Sarcoma botryoides of the cervix; localized adenomyosis uteri; corpus luteum (right ovary); early premenstrual endometrium.

Her postoperative course was uneventful except for the development, upon the sixth postoperative day, of a frequency, urgency, and incontinence of urination. Cystoscopy and biopsy of a small necrotic area in the base of the bladder failed to reveal the presence of any malignant tissue or the presence of a vesicovaginal fistula. Methylene blue instilled into the bladder did not appear in the vagina.

She was discharged in good condition on Dec. 28, 1941, and was referred to the Brooklyn Cancer Institute where she is now receiving irradiation.

#### SUMMARY AND DISCUSSION

First reported in 1854, 94 cases of sarcoma botryoides of the uterus have been recorded in the literature. Of these, 36 have been confined to the cervix. Of a highly malignant nature, the average duration of life is one year after discovery despite all forms of treatment. Among the histologic elements noted are many which are foreign to the uterus, such as cartilage, striated muscle, myxomatous tissue, and sarcomatous stroma. It was primarily our intent, in submitting this report, to record another case of this rare and highly malignant form of uterine tumor. Our own case is especially characterized by its occurrence at an adult age, the presence of constantly recurring cervical polyps with irregular vaginal bleeding, and, in the microscopic picture, the presence of striated muscle. For a complete review of this subject, one need only to refer to the recent and comprehensive report by Glass and Goldsmith.<sup>1</sup>

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The anorectal type of case usually has a stricture though some cases do not. Abscesses, fistulas, and sinuses may be present around the anus. Peritonitis, liver abscess, renal involvement, and systemic manifestations of all kinds may be associated with this disease. The author's experience has been that the operative treatment of this condition must be undertaken in 2 stages. In the first step, a colostomy is done and all abscesses about the anus are drained. This is followed in three weeks by a mucosal stripping operation. The author feels that this same procedure could be used for cases of multiple fistulas.

WILLIAM BERMAN.

## TUBERCULOSIS OF THE VULVA

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**T**UBERCULOSIS of the vulva is uncommon enough to be considered a medical curiosity. In the foreign literature it has been reported at infrequent intervals but in certain of these instances doubt arises as to whether the patient had lymphogranuloma inguinale or tuberculosis of the vulva. In the American literature reports of patients with tuberculosis of the vulva are exceedingly rare (last report 1935). The signs, symptoms, and gross appearance of tuberculosis of the vulva may be almost identical to those of carcinoma of the vulva and herein lies its chief importance for the two are easily confused. Such confusion is

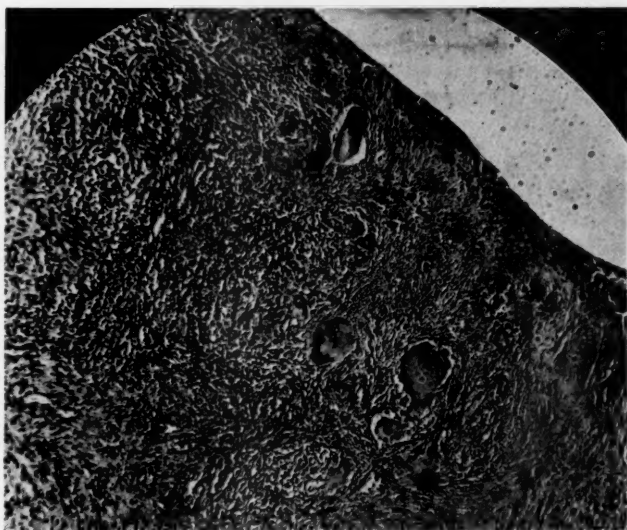


Fig. 1.

unfortunate since simple vulvectomy is usually sufficient to cure the patient with tuberculosis of the vulva, but when carcinoma is present, a groin dissection of the Basset type is indicated. The addition of groin dissection to vulvectomy greatly increases the morbidity and mortality and would be an unfortunate mistake should the patient have tuberculosis rather than cancer of the vulva. A short case report of a patient with tuberculosis of the vulva is here appended:

C. R., aged 44 years, white, married, nulliparous, complained of intense pain and burning in the vulva of eight months' duration. This was associated with an ulceration of the labia which had increased in size progressively. Discomfort was aggravated by micturition. The patient had

never had a prolonged cough, hemoptysis, night sweats, or loss of weight. Roentgen ray examination of the chest was negative. She had had a supravaginal hysterectomy and bilateral salpingo-oophorectomy for leiomyomas of the uterus eighteen months before examination. At that time the vulva was examined and considered normal. At no time was there leucoplakia or pruritus vulvae. Both from history and physical examination there was no suggestion of tuberculosis in the patient's husband. Physical examination of the patient was negative except for a well-healed lower abdominal midline scar and an ulcerated area on the vulva. This involved the major and minor labia and the mucosa adjacent to the vulva. A presumptive diagnosis of carcinoma of the vulva was made.

A biopsy of the ulcerated area did not show malignant tissue. There was instead caseous necrosis with typical tuberculous inflammation and many giant cells. A second and third biopsy revealed identical microscopic structure (Fig. 1). A complete vulvectomy, including the clitoris and the terminal half inch of the urethra, was performed. The cut end of the urethra was approximated to the cut edges of the mucous membrane by interrupted silk sutures. No neoplastic tissues were found on examination of the entire specimen. Convalescence was uneventful, and the patient left the hospital on the thirteenth postoperative day. Two months later a silk suture was removed from granulation tissue around the urethra. Two months after this, persistent granulation tissue was treated by electrodesiccation. The patient is now free from discomfort two and one-half years after operation. Intercourse is possible without pain. On examination there is no ulceration and the tissues are well healed. There has been no inguinal adenopathy at any time.

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In the period between 1912 and 1941, 4,532 mammary lesions were seen at the Portuguese Institute of Oncology; 1,862 were benign and 2,661 malignant. The greatest incidence of pathology was in the 40 to 50 age group. Most patients had initial symptoms at any time within 5 or 6 years, a scattered few having their first symptoms as much as 30 years before reporting for treatment. In 436 cases a swelling or tumor was the first thing noticed by the patient. Stinging sensations, enlargement of the breast were the next most common symptoms.

Trauma was a factor in 100 cases. Diagnosis of a lesion was made in 3 cases fifteen days after simple trauma, in 16 cases from 1 to 8 months after nonsurgical trauma and the remainder were well distributed from one to forty years subsequent to various surgical procedures. Applying strict criteria of relation of trauma to tumor, the author concludes that this relation could not be proved in the majority of cases of the group under study, although in some cases carcinomatous changes appear to have occurred in postoperative cicatricial tissue or in an organized hematoma. The right breast was involved in 302, the left in 313, both in 10 cases of the group. The upper external quadrant was the most common location, seconded in incidence by total involvement. The author presents an excellent and extensive statistical study of treatment, histology, and family histories of carcinoma.

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## AN APPARATUS FOR RESUSCITATION OF NEWBORN INFANTS

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**A**UTHORITIES<sup>1, 2</sup> are now agreed that the treatment of asphyxia neonatorum should consist of proper posture, body warmth, removal of any substance obstructing the upper respiratory passages, and finally the administration of 100 per cent oxygen by a simple, effective and comparatively foolproof mechanism.

Posture and warmth can be managed so readily in all hospital delivery rooms that nothing additional need be added in that regard.

Aspiration and resuscitation methods have been varied and manifold. It is not in the province of this paper to review these methods other than to say that with the replacement of manual methods by mechanical devices, simplification has been sought in order to obviate mechanical failure, and to improve efficiency. The one phase of the subject with which this paper deals is the presentation of a simple mechanical device for the purpose of administering 100 per cent oxygen to a newborn infant after first having thoroughly cleansed the air passages of obstructive material by means of an aspirator attached to the device.

It is true that asphyxia neonatorum is best treated by preventing it.<sup>3</sup> With prophylaxis in its present state, and with analgesia in widespread use, any consecutive series of births will indicate that approximately 15 per cent of the newborn infants show some degree of asphyxia ranging from a mild pallor to cyanosis.

The primary requisite of the ideal resuscitator is that it should be able to simulate natural respiration in volume and in rhythm. The flow should begin and end gently as it does in normal breathing. The device should be adaptable for use on a human being of any age, size, or physical condition. It should be automatic and thus, once adjusted, not susceptible to the whims of the operator. The controls should be few, simple, and easily learned. The resuscitator should be safe, efficient and reliable and should be widely adaptable for use with any gas or gas mixture necessary for resuscitation.

The authors were appointed a committee by the departments of obstetrics and gynecology at Mount Sinai Hospital in 1939 for the purpose of investigating and recommending a resuscitator for use in the delivery suite. Four resuscitators were investigated and subsequently obtained for trial use for from thirty to ninety days. The relative merits of these machines need not be discussed here. Our investigation, together with the unanimous opinion of the staff indicated that the Dann resuscitator was best fitted for our requirements. It is now close to two years during which time this resuscitator has been in constant use. In view of the fact that this machine has never been described, it is being presented herewith and shown in Fig. 1.



Basically, its main working part is a reciprocating, tapered valve which slides gently to and fro past openings through which oxygen (or other gas) flows to and from the lungs. This valve is moved by a gas motor operated by the same source of compressed gas or gas mixture

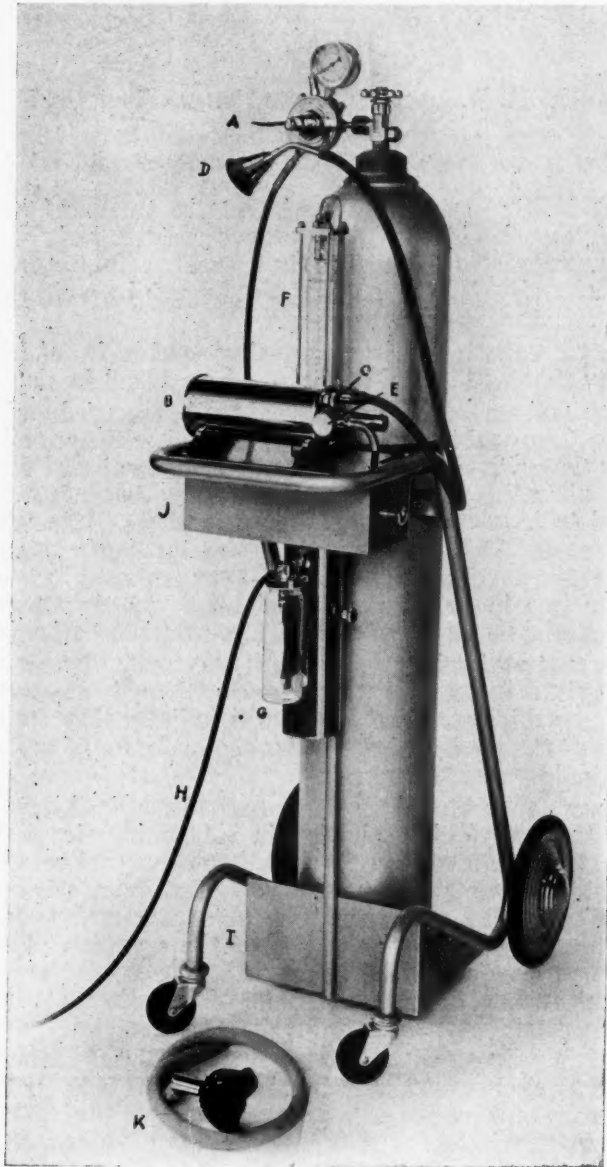


Fig. 1.

that flows to the patient. The rate of pulsation and the volume of each respiration are controlled independently. The operator need not be concerned about pressure—this adjusts itself automatically to the volume of inflow, which is adjusted in each instance to the capacity of

the lungs. Exhalation is completely spontaneous; the lungs empty themselves as they do in normal breathing, by the elasticity of the thoracic cage and of the lungs themselves.

Oxygen is supplied to the resuscitator from a cylinder through a pressure reducing valve (*A*), set to the proper pressure at which the machine is designed to operate. A very small portion of the gas passes to the air motor (*B*). The rate control valve (*C*) controls the flow of this portion of the gas and thus increases or decreases the rhythm of the motor. By means of this valve, the rate is first adjusted to the needs of the patient (from 20 to 25 per minute for infants). Then applying the face mask (*D*) to the infant, the volume control valve (*E*) is slowly opened until proper chest expansion takes place. No further adjustment is necessary. This valve permits oxygen to flow from the pressure-reducing device on the cylinder past a tapered reciprocating piston, through an expansion chamber to the patient. At the end of each inflow, the piston automatically cuts off the flow of oxygen and opens a port in the machine to the outside air which permits free exhalation, without suction of any kind. The piston then closes this port and gently opens another, through which oxygen again flows to the infant.

The simple mechanism of this resuscitator has been so designed that even in newborn infants no delicate manometer has been found necessary to indicate the actual pressure of the oxygen mixture in the lungs. So long as the volume control valve is opened slowly and precisely to the point at which chest expansion occurs (a point easily observed), there is no danger of reaching excessive pressure in the lungs, even in premature infants. The controls on the resuscitator permit the flow to be adjusted exactly to the physiologic needs of the infant. Except for the indicators on the oxygen cylinder, gauges have purposely been omitted from this machine. Our experience with other resuscitators left us with the impression that such gauges provided a false sense of security—because the operator tends to watch the gauge or meter and not the infant. In addition, gauges and flow meters do not account for small leaks which may occur about the face mask. With this resuscitator, the operator gives undivided attention to the patient, adjusting the controls to the response of the subject.

Some members of the staff felt that a manometer would be a helpful addition to the resuscitator. As a result, a sensitive water manometer (*F*) was designed and attached to this machine. It indicates pressures up to 22 cm. of water (16 mm. of mercury) and does not permit the pressure to exceed this level. Through a small valve the manometer may be used or excluded as the operator desires. It is important to remember that it may be necessary for the initial pressure to exceed 22 cm. of water to inflate an atelectatic lung. Once the alveoli are opened, insufflation of the same amount of air will usually give pressures below 15 cm.

Attached to the resuscitator is a special aspirator (*G*). This also operates from the gas cylinder and provides rapid, rhythmic suction which may be varied by the operator from one to 160 cm. of water for preliminary removal of mucous or other material that may block the air passages and prevent ingress of the resuscitating gas. Together with a suitable collecting bottle, this aspirator is admirably adapted for use in the delivery room, in that it can be used as soon as the baby's head is delivered. When so used, the entire resuscitator, which is mobile, is

moved alongside the mother. A sterile glass tube and rubber catheter is available for attachment to the aspirator tubing (*H*). The obstetrician is then handed the catheter already attached to the tubing by a nurse who, at the same time, sets the aspirator in motion. The obstetrician then can aspirate the nose, mouth, and pharynx before completing delivery of the infant. This aspirator has also been used successfully on several mothers, with the recovery of aspirated vomitus from the upper respiratory tract, and with the avoidance of severe complications.

As will be noted in Fig. 1, the resuscitator is attached to a mobile steel cart (*I*) which rolls noiselessly. This cart holds a large oxygen cylinder and occupies a floor space of 20 by 30 inches. It has a drawer space (*J*) for face masks, intubator, and other accessories (adult mask [*K*]).

As previously mentioned, the increasing use of analgesia and anesthesia in parturient mothers has made fetal asphyxia a more common occurrence. Various measures have been employed to initiate respiration in the newborn infant, both manual and mechanical, but none have been so simple, rapid and effective as the gentle pulsating flow of this resuscitator. A particular advantage of this respirator is its ability to expend the atelectatic lung of the newborn infant. Machines in which the pressure only is controlled are often incapable to initial filling of the lungs because this requires greater pressure (owing to the adhesion of the lung surfaces) than subsequent inflations. In this resuscitator the volume is adjusted to the needs of the infant and this, once adjusted, can never exceed the capacity of the lungs. At the same time the machine, when this is necessary, automatically permits enough pressure to be built up to overcome the adhesion of the lung tissues. Thus, once the rate is set, the operator need only adjust the machine for proper expansion of the lung. Spontaneous respiration in the infant usually occurs within a few minutes, often in a few seconds.

This resuscitator is so simple in its operation that the entire obstetric and nursing staff have been trained in its use in a very short time. The only essential knowledge needed to operate the apparatus is a practical understanding of the mechanism of respiration. We feel that any individual who understands the fundamentals of respiration and who has learned how to adjust the two control knobs on the machine can give artificial respiration to the newborn infant with complete safety.

#### SUMMARY

1. The Dann resuscitator is a safe, efficient, positive pressure respirator.
2. It is simple and virtually foolproof in design, having only two controls.
3. The rate and volume of respiration are independently adjusted to the physiologic needs of the infant.
4. Once adjusted the machine is entirely automatic. Its rhythmic, gentle insufflations simulate natural respiration. Exhalation occurs spontaneously.
5. The attached aspirator may be used before full delivery of the infant and should always be used before starting resuscitation. In use, it may be readily alternated with the resuscitator.
6. The simplicity of this machine makes it easily operated by almost anyone.

We are indebted to Mr. Morris Dann (735 Thornhill Drive, Cleveland, O.), designer and manufacturer of this resuscitator for his technical cooperation, and to Dr. M. S. Biskind of New York City for his editorial assistance in the preparation of this manuscript.

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## METHOD FOR CORRELATING DATA FROM MENSTRUAL CYCLES OF DIFFERENT LENGTHS

### A SIMPLE NOMOGRAPHIC PROCEDURE

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**I**N CLINICAL and laboratory investigations of the menstrual cycle, one is confronted with the problem of bringing together data from cycles, which though normal in every respect, differ greatly from each other in length. Thus, an observation made on the fifth day of a cycle of twenty-four days in total length may not be compared, on the basis of

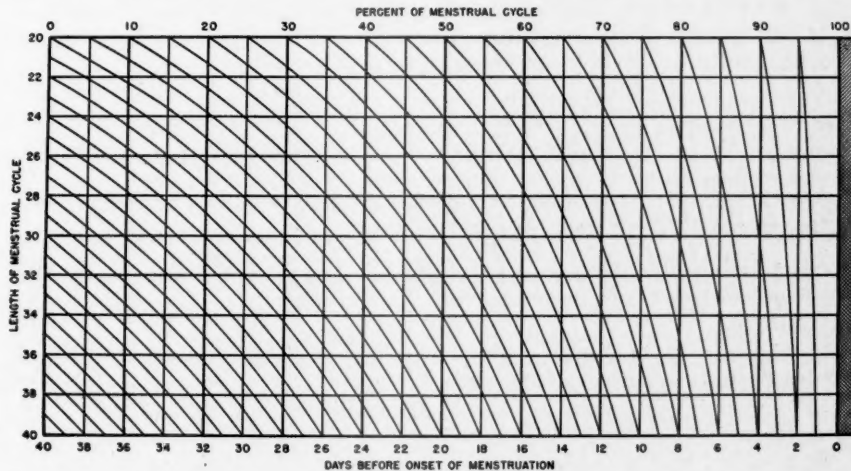


Fig. 1.—Nomogram for determining the percentile value of any day of a menstrual cycle, counting back from the onset of the next menstrual period. To be used for cycles twenty to forty days in duration. See text for description and use of this device.

any known sequence of physiologic events, with observations made on the fifth day of a cycle thirty-four days in length. One is tempted to arbitrarily disregard cycles outside a given range of duration, or to try to discuss a group of miscellaneous data on the basis of a figurative twenty-eight-day cycle. The simple device proposed in this note is no less empirical than the foregoing methods, but it possesses the merit of



making it more easily possible to unify one's data for purposes of comparison, when this is justified.

The basis of the method is that every normal cycle is considered to have a duration of 100 per cent, and any given day thereof represents a specific percentile of the whole. This is exemplified at the top of Fig. 1.

To use this nomogram, two facts and three procedures are required. One must know first, the number of days in a given menstrual cycle and, second, the number of days before the onset of the next menstrual period that a given event, or procedure, in the menstrual history occurs. With these facts, one looks (a) at the bottom legend for the specific day before the onset of menstruation; (b), at the left, for the number of days which that cycle lasted, and (c) one follows the abscissa, from the left, to the point of intersection with the curved line for the desired day, and from the *corresponding vertical ordinate, at the top*, the percentage value of the cycle is obtained.

Two examples of the use of this procedure are as follows: (A) An observation made on the sixteenth day before the onset of menstruation (read at bottom) of a thirty-two-day cycle (read at left), is at the 50 per cent point (read at top) of the cycle, directly above the indicated point of intersection of the three lines. (B) The sixteenth day before menstruation (read at bottom), of a cycle twenty-two days in length (read at left) is at the 27 to 28 per cent point (read at top) of the menstrual cycle. Similarly one may read the position of any other day, or fraction thereof, if one chooses to read that closely.

By use of a similar type of nomogram, one might equally well compare data from periods of gestation of differing lengths within a given species, and possibly between several species.

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**Loeser, Alfred A.: Mammary Carcinoma, Response to Implantation of Male Hormone and Progesterone, Lancet 2: 698, 1941.**

On the assumption that excess of estrogenic substance is a factor in producing cancer of the breast, an attempt was made to counteract this effect by implanting male hormone.

In mice of a strain showing a very high incidence of breast cancer, testosterone propionate was implanted subcutaneously in 10 every three to five weeks while 12 acted as controls. Implantation was not begun until the mice had had three litters. In the treated group 4 and in the control group 9 died of cancer.

In 6 women with a family history of breast cancer who had had their breasts amputated for carcinoma, testosterone propionate or progesterone or both were repeatedly implanted and in 2 progesterone was also given by mouth. In 3, recurrences were present at the time of implantation, and though 2 of these improved temporarily in general health, the progress of the cancer was not checked. In 3 no recurrences or metastases were present at the time of implantation, and none has appeared in the subsequent five years.

It is suggested that male hormone should be implanted in the operation site when the breast is removed for carcinoma, and implantation should be repeated when signs of masculinization disappear.

CARL P. HUBER.



## AN IMPROVED VEHICLE FOR MEDICATION OF THE VAGINA

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ORDINARILY the efficacy of a therapeutic agent is roughly proportional to the efficiency with which it is applied. For skin diseases the dermatologist has a wide range of lotions, ointments, powders, wet compresses, etc., which keep the active agent in contact with the lesion for long periods of time. However, for treating affections of the vagina, lined with stratified squamous epithelium somewhat resembling skin, we have heretofore been limited to the use of douches, injections, tablets, and suppositories which are quite transient in their contact with the vaginal lesion. Tampons are used to treat the cervix, but their effect on the vaginal mucosa is one of prompt irritation, and they soon become malodorous. In recent years, insufflation of powders into the vagina has achieved considerable popularity, and this report deals with an attempt to improve such methods.

It seems logical to assume that a satisfactory vehicle for applying medication to the vagina should fulfill at least the following requirements:

1. It should be harmless to the patient.
2. It should be demulcent and antipruritic.
3. It should not soil or damage clothing.
4. It should be inexpensive.
5. It should be easy to apply.
6. The patient, herself, should be able to remove it.
7. It should remain in situ without the aid of tampons, pads, or cups.
8. It should gently maintain separation of the walls and folds of the cavity.
9. It should remain in contact with all surfaces for a prolonged period of time.
10. It should absorb secretions and discharges.
11. It should adsorb all odors.
12. It should provide a pH which is optimum and should maintain this pH for a prolonged period of time.
13. It should provide a medium for the growth of the normal vaginal flora.

Such a vehicle, for which the descriptive term "Tamplast"\* is suggested, has given satisfaction in my office practice for more than three years. It is composed of lactose, citric acid, finely divided kaolin, finely powdered hemicellulose of *Plantago ovata* and the exudative gum of *Anogeissus latifolia*. The finished product is a finely divided, whitish gray-colored powder of almost fluffy consistency with little or no distinguishable odor. This powder, when mixed with sufficient water to make a tenacious gum, has a pH of 4.0 to 4.5 due to its citric acid content. The lactose serves as a medium for growth of normal vaginal flora. Finely divided kaolin is one of our best adsorbents for odors.

\*Prepared by Marshall and Bell, Atlanta, Ga.

The hemicelluloses of *Plantago ovata* and karaya gum both have the capacity of absorbing several times their volume of moisture and are valuable demulcents.<sup>1</sup> Karaya gum may be omitted in allergic individuals, the proportion of more extensive *Plantago ovata* being doubled.

The powder is applied by means of any powder blower, preferably with the patient in the knee-chest position, after the vagina has been dried with cotton pledgets. The patient is instructed to take a saline douche under pressure sufficient to distend the vagina just before her return to the office at the end of twenty-four to seventy-two hours. Such a douche will easily remove all the material. In the case of the inept woman who either cannot or will not take a douche properly, it



Fig. 1.—X-ray of pelvis of nullipara forty-eight hours after insuflation with "Tamplast," containing 20 per cent barium sulfate.

is well for the physician to assure himself that the material will be removed. A patient may also neglect to take her final douche after dismissal if she feels that she is already cured.

If douching is omitted, the vagina will be found to contain a soft, plastic mass which adheres gently to, but may be easily removed from, the surfaces of the cavity. If carefully removed en masse, it will be found to present the shape of the partially distended vagina, showing many of the rugae, etc. The pH of the surface of this cast will usually average 4.5, even though the vaginal pH at the beginning of treatment were considerably higher. The vaginal walls and portio will be found to be almost dry and of healthy appearance. There is virtually no odor to the mass removed as late as seventy-two hours even in cases of trichomonas vaginitis.

The vehicle will remain in situ for as long as twenty-four to seventy-two hours without the aid of tampons, pads, etc., often even in women with markedly relaxed perineal support (Fig. 1). The material acts as a demulcent and antipruritic, giving almost instantaneous relief, extending over the entire period of its use. The powder can advantageously be blown over the urethra and vulva, the patient being instructed not to void for several hours. Discharges are entirely absorbed by the medium, giving the patient immediate and lasting relief from this annoyance. The fastidious woman is also grateful for the prompt disappearance of all odor due to its adsorption in the mass.

Various therapeutic agents such as diodoquin, silver picrate, quinine, vioform, and other protozoacides may be added to the vehicle by substituting one of these for portions of the lactose up to 10 per cent. Diodoquin, 5 per cent, and vioform, 5 per cent, have given satisfaction in the treatment of trichomonas vaginitis.

Absorption of the discharge enables one to use silver picrate and even gentian violet intravaginally without the objectionable soiling of the patient's clothing and bed linens.

I have had limited experience with the use of this medium in monilia vaginitis, but in such cases the citric acid should be replaced by an alkali, such as aluminum hydroxide, to elevate the pH to about 7.5 or 8.0, and the lactose should be omitted. The formula described by Minnich<sup>2</sup> (sodium perborate, sodium lauryl sulfonate, thymol and aromatics) in proportions up to 6 per cent has given excellent results. It has been used without harm in the last months of pregnancy, giving complete relief from symptoms even when clinical cure was not obtained.

No ill effects have been observed from the use of this medium, either acid or alkaline, in a large number of cases. It probably should not be used in the presence of acute cervicitis of any kind, but it has been used to check the irritation of the vagina from chronic cervicitis and occasionally after separation of the slough of the cauterized cervix. In the experimental stage, one patient was insufflated with diodoquin in the acid medium once weekly for three weeks. No douches were used, the cast being removed instrumentally at the end of each seven-day period. The surfaces of these casts all presented a pH of 4.0 to 4.5 when removed, and there was no distinguishable odor. A vaginal smear taken when the last cast was removed at the beginning of the subsequent menstrual period was perfectly normal.

It is my impression that with the use of this vehicle the dosage of a therapeutic agent can be reduced and at the same time the number of treatments decreased, which together with longer intervals between treatments is of considerable economic importance. In the case of medicaments such as the estrogens, the powdered estrogenic substance may be insufflated into the distended vagina in the knee-chest position and the vehicle then blown into the cavity. This results in a plastic cast coated with estrogenic substance which remains in contact with all surfaces of the vagina for a prolonged period of time, greatly enhancing the local effect on the epithelium, hastening the appearance of the typical estrogenic reaction, and substantially reducing the cost of treatment.

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## Special Articles

### CONTRIBUTIONS OF STUDIES ON PRIMATE ANIMALS

#### TO GYNECOLOGIC THOUGHT\*

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(From the University of Illinois)

IT MAY be presumptuous in me to attempt to diagnose gynecologic thought as of 1942 on the items I am going to discuss. I have found it profitable, however, to try to keep abreast the theoretical aspects of gynecology, partly through the literature but above all through my friends in the profession. It is certainly true that today clinician and laboratory experimenter are in close touch with each other. This is mutually beneficial, as has long been shown. The science of endocrinology owes its beginnings to the clinician, and clinical data continue to point to significant problems which animal experimentation aims to elucidate and thus to guide medical practice. It is my purpose to call attention to some contributions which apes and monkeys, particularly the rhesus monkey, have made to gynecology.

I realize further that, in a sense, I am bringing coal to Newcastle, speaking on this subject, since so many contributions to our topics have come from your laboratories. I need mention only Daron, Markee, Rossman, and others who worked with that master of the subject Bartelmez, who enjoyed the cooperation of clinicians like Culbertson and Brewer; Ivy, Rudolph and Danforth for their brilliant work on parturition, Klüver on behavior; Davis on vaginal reactions to hormones.

If one plots by year of publication, the literature list in Zuckermann's interesting little volume *Functional Affinities of Man, Monkeys and Apes* (1933), he will be struck by the sudden upswing of the curve with the turn of the century, particularly in the last decade of the period covered. It appears, too, from Ruch's *Bibliographia Primatologia* that more papers have been published on primates in the last two decades than in all previous history.

The modern studies have continued the basic morphologic studies of the nineteenth century, neurology being the chief growing point in this field, though it must be added that, in the modern spirit, functional aspects have received prime emphasis. The physical anthropologist has gathered his data from detailed study of primate skeletons of all orders (A. Schultz) and from dissection of cadavers, in order to determine more definitely primate relationships. Studies in behavior (Yale Laboratories) served to lift the apes and monkeys above the run of lower mammals, while studies in sex behavior and other forms [social behavior, both under laboratory conditions (Ball, Yerkes) and in the field (Carpenter)] have added considerably to our knowledge of our nearest of kin in the animal world. Reproductive processes, particularly menstruation, embryonic development (Heuser and Streeter) and

\*Presented at a meeting of the Chicago Gynecological Society, January 16, 1942.



placentation (Wislocki and Streeter) have been of special value to the clinician, as will appear below.

On the basis of all of these data it is apparent that seriation of the apes and monkeys on the basis of similarity to man depends on the character chosen: hand, foot, skull, pelvis, or the scores of indices the physical anthropologist has invented. Man is "primitive" with regard to one character, highly specialized with regard to another. On the whole, however, adding up scores, we must conclude, first, that the primates stand out from all other mammals and, second, that by and large the great apes or anthropoids (chimpanzee, gorilla, or orangutan) are more like man than the monkeys, the much studied chimpanzee perhaps the nearest to man of all of them. In this lecture some items will be mentioned substantiating this generalization.

That apes and monkeys menstruate at approximately the same intervals as women was first demonstrated by Cuvier in 1825. Since the publication of Corner's study of laboratory-kept rhesus monkeys exactly a century later, it has become apparent that the process is identical in monkeys, apes, and man. In this lecture I aim to touch on some of the high points of the physiology of the reproductive process of primates and with greater emphasis on my own researches perhaps than these deserve.

#### LENGTH OF MENSTRUAL CYCLE

Up to very recent years, the gynecologic world adhered to the idea that the "normal" woman menstruates at regular intervals of a lunar month. This insistence had its origin in the superstition of lunar control of the cycle, which even so objective a scientist as Arrhenius tried to substantiate. It is true that the average of numerous cycles of both the rhesus female and of women figures out to twenty-eight days. But here the "lunar influences" cease; the chimpanzee menstruates at intervals of about thirty-five days, while the estrous cycle of animals is of various lengths: four to five days in the mouse and rat; sixteen in the guinea pig; twenty-one in the pig, the cow, the mare; twice annually in the cat; and once annually in many wild forms. Moreover the first day of these cycles falls at random upon any given phase of the moon.

As soon as a sufficient number of female monkeys had been studied in various laboratories (the records of the Carnegie Colony now number thousands of cycles), with daily examination of the animals, it became apparent that no monkey female was absolutely regular, even the most fertile of them. Within the last decade it has become practically axiomatic in gynecologic circles that women, too, are far from "regular," and physicians now no longer take a woman's general impression based on all too faulty memory, of her "regularity" but are requiring calendar records of their patients. This is useful in itself, for from such records he can learn something, since very irregular periods may be associated with other evidence of faulty organ functioning. On the basis of my monkey records, I can agree with Rock's contention, based on clinical experience, that nonovulating females tend to be more irregular than fertile, ovulating individuals. With the spread of the "safe period" or "natural" method of birth control, which many patients insist on practicing, it has devolved upon the physician to offer advice based on the best information obtainable. Since it is assumed that the day of ovulation may shift with the onset of the succeeding period, in other



words, is delayed in the longer cycles, accurate records of the menstrual behavior of the patient become all the more necessary.

I think you will agree, therefore, that the former conception of regularity in menstrual schedule is a relative and not an absolute concept.

#### THE PRIMATE UTERUS

Fortunately, the menstruating organ, the uterus, is similar in structure in the higher monkeys, apes, and man, and this generalization applies to all of the details so far studied. It is possible to check many items and make direct comparison between the human tissues and those of monkeys. But the latter still offer the advantage of availability for biopsy and autopsy at the experimenter's will. There is the added advantage in the use of the monkey that it is possible to make vascular injections in a manner that can never be done in the human being and thus to learn vascular patterns in important structures.

One outcome of the monkey studies now in progress as a cooperative effort of Corner, Bartelmez, and myself will be the determination of exact time relations in the transformation of the endometrium after ovulation. Is the response variable or is the endometrium at twelve days after ovulation the same in all cases? We may state that a score of specimens of this period where the exact day of ovulation is known show great similarity in their histologic picture.

#### HORMONAL CONTROL OF MENSTRUATION

In response to ovarian hormones, the uteri of monkey, ape, and man are likewise similar. The monkey has, for that reason, proved invaluable in the search for the cause of menstruation. This problem is far from solution, although some of us have from time to time, in misplaced enthusiasm, felt that we were pretty close to the goal.

The gonadal hormones were first exploited, then extragonadal factors were invoked: anterior pituitary, posterior pituitary, the adrenal cortex, the adrenal medulla.

Beginning with E. Allen's classical experiments on the production of uterine bleeding in castrates that had received estrin, the search was on. We now know that the normal "Hitschmann and Adler" picture of the uterine cycle may be reproduced by estrogens accompanied, as in the normal cycle, by progesterone. Bleeding, moreover, follows soon after the cessation of treatment, just as after the removal of an active corpus luteum.

All these facts fitted in beautifully with the basic events of the menstrual cycle. But it was soon found that one could inhibit the bleeding with testosterone as also with desoxycorticosterone. Bleeding followed cessation of action of these hormones. Finally these hormones were found to stimulate growth of the endometrium, as indeed will progesterone alone, without priming with estrogen.

Perhaps it is an academic question, but it is often raised: which is the dominant hormone in the menstrual cycle, estrone or progesterone? Since nonovulatory cycles are indistinguishable outwardly from ovulatory ones or in the behavior of the blood vessels in intraocular transplants (Markee), progesterone is superfluous, unless, indeed, atretic follicles do produce progesterone. The problem is further complicated by the fact that in the ovulatory cycle, in the presence of an active corpus

luteum; there is a second rise in estrogen output, so that one may contend that here, too, menstruation is due to estrogen deprivation.

Before the last word is said on the relation of the steroidal hormones to menstruation, it will be necessary to determine the metabolism of the hormones in the body. Menstrual phenomena are pretty nearly identical in man and monkey, yet in the metabolism (destruction, transformation) of progesterone as well as estrogens the two species differ markedly. Androgens and products of adrenal cortex coming into the picture further complicate the theoretical aspects of the problem.

#### THE SPIRAL ARTERIES

Menstruation is a vascular phenomenon. The changes in the blood vessels leading to menstrual bleeding may be seen in intraocular transplants of the endometrium according to the Schochet method perfected by Markee. This investigator has given us a clear picture of the behavior of the blood vessels, spiral arteries, capillaries, and veins preceding and accompanying the menstrual flow. For these basic studies, of course, the monkey is indispensable.

Among cyclic changes in somatic blood vessels we must mention the increased fragility of the cutaneous capillaries described by Brewer. But no such general rule can apply to the arterioles of the endometrium, because, as Markee has dramatically described the process, menstrual bleeding is a strictly local affair, involving single fields supplied each by its spiral artery. Neighboring fields may not be involved until hours or days later. Under the endocrine theory of menstruation, we should expect identical response at all points at the same time.

Markee's studies have further emphasized the fact that for menstruation to occur there must first be endometrial growth (in response to hormone stimulation), then regression (due to hormone withdrawal). The regression seems essential. Menstrual bleeding does not follow regression of the endometrium in the rabbit, however, under the same circumstances; this leads one to inquire: what peculiarity of the primate endometrium is bound up with the menstrual phenomenon?

The answer to this question, so far as morphology can give an answer, lies in the spiral arteries, the structure of which has been largely cleared up by Daron. These arteries doubtless have physiologic properties peculiar to themselves, but about that we as yet know little. We do know, however, that rabbit and guinea pig endometrium does not bleed, although the transplants regress after a drop in hormone level. The bleeding that has been described in rabbit uteri (Zondek) after large doses of estrogen is pathologic and has nothing to do with menstruation.

#### THE VAGINAL CYCLE

Monkey and man further closely parallel each other in the similarity of reaction of the vaginal mucosa to estrogens and progesterone and the sequence of changes in the menstrual cycle. That there is a clear-cut cycle in the monkey was revealed by vaginal biopsies studied by Davis. Whether there is a similar cycle in women is still under dispute, with a majority of the workers claiming to have demonstrated a cycle. On the basis of vaginal smears, however, stained by the differential method of Papanicolaou as modified by Shorr, it is now possible to draw a perfect parallel between the monkey and man. This conclusion

is the outcome of a cooperative research by Dr. Inez de Allende of Argentine, Dr. Shorr of New York, and myself. Some of the facts are these:

As ovulation approaches, leucocytes and basal epithelial cells are present in the smear in reduced numbers down to zero, and large scale-like cells take their place. Several days before ovulation there appears a cell type thus far overlooked; it is present but one day, except in the absence of ovulation, when, if it appears at all, it persists for several days. It can be produced in response to estrogen administration in castrated monkeys and menopausal women. In both monkey and woman, in ovulatory cycles, in correlation with the second peak of estrogen secretion, this cell, which I would like to call the "Shorr" cell, reappears. This holds for both species. The details will be published later.

#### THE MAMMARY GLAND CYCLE

The occurrence of cyclic changes in the human breast parenchyma is likewise both affirmed and denied. For the monkey Speert has been able to demonstrate such a cycle, but only by means of successive biopsies on the same animal in the same menstrual cycle. After studying and classifying hundreds of biopsies taken by Speert and myself for various purposes at the Carnegie Colony, it was found that the individual variation in the breast often exceeded the cyclic changes in the same animal. Unlike the uterus, the breast showed great variation under the same hormonal stimulation, reflecting conditions immediately preceding a given moment of biopsy. On the contrary, the quickly regenerating endometrium reflects the endocrine level of the moment.

These facts would explain the conflicting results obtained in most human studies and also Speert's agreement with Rosenberg, who based his conclusion on successive biopsies on the same woman.

#### THE CERVIX UTERI

No one has as yet, to my knowledge, made successive biopsies on the monkey cervix comparable to the studies of Wollner in the human being. I have a collection of cervices, however, taken from autopsies; from a cursory study of these, it appears that there is a shallow cycle perhaps even less marked than that of the mammary gland.

A priori, one must postulate a cycle demonstrable histologically because of evident cyclic changes in the viscosity of the cervical secretion. For both in the monkey (Lamar and Shettles) and in women (Lamar, Shettles and Delfs) the otherwise rather thick cervical mucus changes suddenly and for but a day or two in each cycle to a thin fluid of such low viscosity that sperms penetrate at a rate of a millimeter in three minutes. This condition was frequently found also in the premenstruum, again doubtless in response to the second rise of estrogen level characteristic of the ovulatory cycle.

#### TIME OF OVULATION IN THE MENSTRUAL CYCLE

Let us not agree from the double peak of estrin level that there are two ovulations ("three in young girls") as Samuels contended. To do so we should have to discard all the sound information that has been gained from thousands of laparotomies as well as controlled observations on ovaries and uteri of women and primate animals.

I shall not discuss at length the problem of the time of ovulation in the menstrual cycle, having little to add to former discussions. The work in the monkey, including the hundreds of ovulations recorded at the Carnegie Colony, has certainly influenced gynecologic theory on this subject and stimulated observation and experiment. In the monkey, ovulation occurs almost never before the eighth day or after the sixteenth day, twelve or thirteen days being average. The time may be a little later in women, especially in longer cycles, as it is later in the chimpanzee, which has a thirty-five-day cycle and ovulates around the seventeenth or eighteenth day.

It is more than an academic question to ask if and how often does ovulation and hence possible conception occur at a time closer to the menses than the schedule experienced by the monkey or that suggested by the Ogino-Knaus theory for women. If we can experimentally change the ovulation day, perhaps we should remember that nature has already, at some time or other, performed such an experiment. We can indeed hasten ovulation with gonadotropes; twice in monkeys of the Carnegie Colony Dr. Ball caused a delay in ovulation, once with estrogen and once with testosterone injected in the middle of the cycle.

A parallel case is offered by the phenomenon of superfetation and I must confess that I used to argue that there were no authentic cases of such an event and that ovulation could not occur during pregnancy. Since Snyder and Wislocki have shown how superfetation can be produced at will, we may as well believe that by some anomalous endocrine balance superfetation occasionally occurs in nature. The mare frequently ovulates during each pregnancy although superfetation is unknown in that species, though some day a case will doubtless be found. And so the question of superfetation, as well as that on conception near or even in the menstrual period, in my judgment is an academic one and of theoretic value only, though I admit it looms large in the minds of couples practicing the safe period.

In general, however, it is certainly true that, in giving advice to his patients, the gynecologist will stick pretty close to the schedule of the monkey's alternating fertile and sterile periods of the cycle.

#### NONOVULATORY MENSTRUAL CYCLES

Gynecologists have likewise generally accepted the existence in women as in the monkey of the nonovulatory type of menstruation, conveniently termed "pseudomenstruation" (Schroeder). The existence of this type was long ago shown to occur in nature by Heape and by van Herwerden and in laboratory rhesus monkey by Corner (1923). An overwhelming number of cases, thousands of cycles, have accumulated in my protocols at the Carnegie Colony. In the summer the nonovulatory cycle is the rule.

The recognition of the condition in women seems a step in advance, for it is something to realize that a woman may be perfectly normal and yet skip an ovulation now and then. It is of further help in classifying sterility cases which seem otherwise healthy and normal.

What to do for such women is, of course, difficult to say. Rhesus monkeys have served as subjects for experiments in this field but with only partial success. Less than a dozen cases were helped in 150 attempts to cause ovulation with gonadotropes. If the chances are as



good as 1 in 15 (and they seem to be) of curing sterility in women by means of gonadotropes, the gynecologist is probably justified to experiment further in this direction, particularly since no permanent damage has been shown to occur from the treatment.

#### PREGNANCY

Certain parallels may be drawn between man and monkey with reference also to the pregnancy cycle. I shall speak of the mechanism of implantation, the structure of the definitive placenta and the output of chorionic gonadotropes.

*Implantation.*—There is every reason to believe that cleavage and vesicle formation in man will be found quite comparable to that in the monkey when the story is now complete. The youngest human ova (Miller, Hertig I and II) are already well implanted. The chimpanzee Yerkes A is only slightly younger. The monkey vesicle begins to attach to the uterine epithelium nine to twenty-four hours after fertilization. For the present it seems safe to adopt this schedule for man, inasmuch as no fact surrounding the young human embryos thus far discovered is at variance with this assumption.

Implantation begins by virtue of the invasive action of the trophoblast, which destroys the maternal tissues. There is every indication that the tissues are digested in situ and utilized by the embryo. The syncytium, the lacunae in the trophoblast, and other features in young monkey and human embryos and in the only chimpanzee embryo known are the same. There is a minor difference only in that the ape and human vesicles dig in deeper, become "interstitial," growing villi on all sides, whereas the monkey ovum remains superficial. The definitive placenta is identical in all three species.

The invasive action of the trophoblast continues for nearly a month when the villi become vascularized and an orderly exchange between mother and fetus is possible. The "parasitic" stage is common to all three species and ends with the establishment of the fetal circulation.

#### PLACENTAL HORMONE

Common to all three species, also, is the production and excretion in the urine of a chorionic, gonadotropic hormone. First discovered by Aschheim and Zondek in man, it has since been found in the chimpanzee as well as the monkey and seems to be the same substance in all three species. In the monkey, however, it is recoverable in the blood or urine only for about a week, first appearing, as in women, about the time of the first skipped menses or about eighteen days after conception. In the chimpanzee no hormone is found in the second half of gestation. It is truly astounding that so small an object can have so large an effect that 5 c.c. of the mother's urine has a sufficient amount of hormone to give a positive reaction in a twenty-one-day-old rat.

It should be added that in no other animal than the primates has chorionic hormone been found in the pregnancy urine.

#### THE PLACENTAL SIGN

At about the time when the gonadotrope appears in the urine of the pregnant monkey, uterine bleeding occurs which simulates menstruation but is usually much lighter. This is the so-called placental sign.



It was absent once in each 100 pregnancies in the Carnegie Colony. It occurs in women also, and is responsible at times for miscalculation of the date of delivery by one month. I am told by Dr. Alan Guttmacher that, in the history of 200 private patients who did not abort, bleeding or staining occurred in early pregnancy in 42 cases, in only 15, however, as early as the twenty-fifth to the fortieth day after the last menstrual period. In the monkey, blood comes from uterine glands receiving blood from vessels that have been tapped by the erosive action of the trophoblast. Because of the interstitial implantation in man, one would expect that the human uterus would lose less blood into the uterine cavity than is the case in the monkey with its superficial type of implantation.

*Ovariectomy During Pregnancy.*—Concerning this problem, the clinical experience points to the conclusion that certainly after the second month of pregnancy the corpus luteum is no longer needed for the maintenance of pregnancy. Corroborative evidence is found in my experiments with the monkey. In one report I showed that it was safe to remove both ovaries from the thirty-first day on. How much earlier, was the question which remained. Theoretically, the answer was about the twenty-fifth day, for Corner, Bartelmez, and Hartman showed that about this time the corpus luteum begins to involute to a point at which it remains almost stationary the rest of gestation. In one experiment (Monkey 637) which I reported, gestation went on in spite of castration on the twenty-fifth day, although an irregular bleeding and a blanching of the sex skin indicated a lack of hormone; but the animal recovered from this "threatened abortion" and gave birth to a normal baby at the exact day expected on the basis of the average period of gestation for the rhesus monkey, one hundred and sixty-five days. The ovaries, serially sectioned, are in my possession.

But this story has a sequel. The female nursed her baby normally, maintaining a brilliant sex skin (estrogen effect?) and bled after four months' lactation. What hormones conditioned this bleeding? Ovarian, from remnants of ovary or accessory ovary? Adrenal cortex? We shall see. Again we have the advantage over the clinician: We can, after a period of observation perform a complete autopsy at our convenience and check any theories we may have developed concerning this anomalous case: uterine bleeding in absence of ovaries.

*Rate of Development.*—For the first month the rate of development of the monkey and the human fetus is practically identical, we believe. I have utilized this generalization to line up the hundred-odd known human embryos of the first month and estimated their conception age (*Time of Ovulation in Women, Appendix*). After the thirtieth day, the monkey grows faster than the human fetus; the lines cross about the one hundredth day (Schultz).

#### SOME DIFFERENCES

*Hormone Metabolism.*—It is a striking fact that, notwithstanding the similarity of response to the steroidal hormones in monkey and man, what the organism does to the hormones differs greatly. Progesterone is not transformed into pregnanediol and, like estrone and estradiol, seems to be largely oxidized or at least does not reach the urine in amounts exceeding 5 per cent of the amount administered. An intermediate condition seems to obtain in the chimpanzee.

*Prolan.*—The pregnant monkey excretes anterior pituitary-like gonadotrope or "prolan" only from the eighteenth to the twenty-fifth day, the chimpanzee until about the one hundredth day, women throughout pregnancy, on a low level, except for a tremendous peak around the sixtieth day. The characteristics of the hormone seem, however, to be identical in the three species (V. S.).

*The Vaginal Mucosa in Pregnancy.*—The human vagina maintains a fairly thick, stratified mucosal lining throughout pregnancy, whereas in the monkey this assumes infantile thickness (Davis and Hartman). Since estrogen secretion seems to be maintained throughout pregnancy in the monkey (von Wagenen and Dorfman) as in women, the differences just mentioned are difficult to explain. Since progesterone antagonizes the action of estrogen on the vagina, and as the monkey "uses up" its progesterone, it is possible that the monkey vagina receives more progesterone stimulation than does the human vagina in the latter half of pregnancy. The cervix uteri, however, shows an estrogen rather than a progesterone reaction, closely simulating the human condition at parturition.

*The Decidual Reaction.*—In the monkey it is the uterine epithelium, as in the bitch it is mainly the glandular epithelium, which gives the "decidual" reaction by enlargement and multiplication of the constituent cells. The "placental plaques" are, in spite of active mitosis for a period, ultimately consumed by the ovum without leaving a trace. In man the "decidual cells" are enlarged connective tissue cells of the stroma, as in the rodents where the reaction results in large placentomas. The end result in man and monkey is, however, the same, a "primate" placenta with one-layered villi dipping into intervillous spaces filled with slowly advancing maternal blood.

The differences between monkey and man, so far as reproductive physiology is concerned, would seem of minor, the points of similarity of major, importance, which should give the monkey a high score as an experimental animal for the gynecologist.

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## DISCUSSION

DR. GEORGE W. BARTELMEZ (by invitation).—Dr. Hartman's monograph on the rhesus monkey, which deals with the nonpregnant and pregnant cycle, represents the most detailed and authoritative information we have for any primate.

I would like to call attention to just one feature which has impressed me in his presentation, that is the experiments in which the time of ovulation was set back by the injection of hormones. In nonpregnant monkeys we have seen animals in which a series of normal cycles followed one another and then for reasons unknown, nothing happened for a longer or shorter period. In several of these animals the characteristic reddening of the perineal skin which is frequently associated with the growth of the Graafian follicle failed to appear as expected. I quote one case from Dr. Rossman's records: Twenty-eight days after the onset of a period the sex skin began to brighten up, reaching a maximum after seven days. Three days later the color began to fade. Nine days after this menstruation began, that is, forty-seven days after the previous onset. At autopsy on the first day the uterus and the corpus luteum showed a typical first day picture. Schroeder and others have recognized the occurrence of a similar phenomenon in women, and Markee in his observations on the growth of transplants in the eye of the rhesus monkey has also seen long postmenstrual phases of inactivity. His transplants failed in these instances to grow for various periods of time postmenstrually and then growth was resumed. The occurrence of such phenomena means that in any given case it is impossible to say precisely when ovulation will occur. Dr. Hartman's data prove statistically that ovulation is most likely to take place at the middle of the cycle, but postmenstrual periods of inactivity may intervene, and as a result, ovulation may occur any number of days after the onset of a period.

DR. M. EDWARD DAVIS.—Dr. Hartman's work has helped to pave the way for a better understanding of human physiology of reproduction and its many pathologic variations.

Embryology was in a dormant state prior to the founding of the primate colony by Dr. Streeter, Dr. Hartman and their associates at the Carnegie Institution of Embryology. The human material available for study was far too incomplete and often in such a poor state of preservation that there were large gaps in our knowledge, particularly during the early days of gestation. Even the age of many of the well-known embryos was in question. To remedy these defects it was necessary to have normal primate material representative of definite periods. To provide such a source of accurately timed specimens it was necessary to create a normal and healthy environment in which these laboratory animals could live healthy lives and breed normally, to study the entire reproductive career of the rhesus monkey, to develop experimental methods and to follow cyclical changes in the ovary and the uterus. When I first saw Dr. Hartman palpate the ovary of a monkey and describe a mature follicle, I knew that he was a visionary, but I

soon learned that his arduous application to his problem had developed unusual skill in this delicate task.

Numerous perfect embryos and their gestational sacs of known age provided the embryologists with a complete story of primate implantation and the very early development of the embryo. This monumental work provided the impetus for the fruitful contributions of clinicians in this field during the past few years. The magnificent embryos of Hertig and of our own Brewer have aided in these classic contributions. Today, the fascinating story of early implantation and early growth of the embryo has been securely established.

Obviously, although the embryology of the primate was the incentive for the work at Carnegie, the entire reproductive function provided many problems. Careful data concerning ovulation, menstruation, and their correlation were collected over many years under the most ideal conditions. The endocrinal control of the cyclical changes incidental to the reproductive function was investigated. The solution of these many problems was directly reflected in a better understanding of the normal physiology of human reproduction and the many pathologic deviations which produce the gynecologic disease with which we are confronted. The cure of some inflammatory conditions of the lower reproductive tract was the logical sequel of the demonstration of the estrogenic control of the vaginal mucosa. Dr. Hartman and his many co-workers have thus pioneered many of the achievements in gynecology.

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## PREPARED PARENTS—THE CORE OF CREATIVE FAMILY LIVING

HAZEL CORBIN, R.N., NEW YORK, N. Y.

**I**N THESE days of conflict, the differences between man and man, between ideas, ideals, and ideologies are so frequently stressed that we fail to see the common ground upon which we all stand.

So in our field of endeavor for human betterment, we tend to emphasize the differences rather than the common goals toward which we are all striving.

What is our common goal?

Ask the doctor, the nurse, the public health worker, pin them down to basic facts. Ask the social worker, pin her down to the basic things, not the day-by-day aims. Ask the minister, pin him down to basic realities, not the preaching of creeds or rituals, not traditions or visions. Ask the teacher, pin him down to the basic things, not the teaching of facts, or theories, or syllogisms. Ask the soldier, pin him down to ultimate realities, not the winning of this battle nor the annihilation of that enemy. He will tell you, as will all the others, that the end of his work is a strong nation, a strong social system so that strong family life, the basic unit of our free, civilized society, may flourish. That is our common goal.

In the mists of struggle and strife and competition, we frequently miss that goal; we strive for some fetish which we, in our enthusiasm and nearsightedness, have set up. We waste energy and effort, brains



and brawn. We are like a group of disunited allies, fighting the same cause, but unwilling to trust each other, to carry out a unified campaign of action.

For years, each group among us has had an ax to grind, an emphasis to put upon a special field of interest. The group with the most eye-catching phrase, which presented its case most enticingly, secured the attention and the action of the public. The result has been that some phases of the work for sound family living received overemphasis and other equally important, or perhaps even more important, phases received underemphasis.

In one community, perhaps, the need for sanatoria for tuberculous patients might have been most attractively and forcefully presented. In that particular community there might have been more crying needs to which the public paid little or no attention because those needs lacked vigorous champions.

In another community, it might have been a greatly overemphasized campaign for more funds for the control of infantile paralysis, or a pressure group for prenatal clinics unrelated to adequate delivery service. In other communities charity organization groups or housing associations or prison reform societies pressed their claims most successfully for public interest and support.

This struggle and competition for public attention with its emphasis on the dramatic had its other and more pernicious aspects. How avidly various groups presented their cases only to find that suddenly the basis of their appeals had been swiftly and effectively thrown into the scientific ash can. Facts were facts no longer and public enthusiasm sometimes turned into public antagonism or apathy.

We heard such slogans as, "A clean tooth never decays" and "Be healthy—take a bath at least once a week"—and then suddenly we heard them no more.

The egg and milk cure for tuberculosis had its advocates, but they vanished when science proved that the disease is caused by a germ and requires more than diet to combat it. Then came the outdoor life, fresh air, outdoor sleeping tents and pavilions amid the snowy peaks of the Adirondacks or the dry wastes of Arizona. And great health resorts grew up in these localities. People just took for granted, under the tutelage of propagandists, that unless you went to those spots on the map your chances for removing the spot on the lung were very few indeed. Then again the chorus was changed. "Why go away?" became the theme. "You can get well in a local sanatorium." In response to this new emphasis, a great new system of local sanatoria for tuberculosis has grown up and the once popular health resorts have languished.

Or take the field of maternity care. "Go to the hospital. Have your baby in a hospital!" was shouted from the housetops from coast to coast. Somehow in the enthusiasm for hospitalization and the struggle for the public interest, the million and more mothers who had no access to a hospital of any kind were forgotten, and many a mother had her baby with unnecessary fears and dread in her heart, because she lived too far away from a hospital or had no money to go to a hospital. Then, suddenly we heard another chorus and it came right from the hospitals themselves. Said the American Hospital Association, "The safest place in the world to have a baby is a good hospital—but the most dangerous place is a poor hospital!"



Can you blame the minds of John Q. Taxpayer or Constance Contributor for being addled and confused? But in addition there was confusion added to confusion. Most of the social reform campaigns began on a negative note. Poverty, sickness, graft, all these have much more of the dramatic in their appeal than health, honesty, economic sufficiency. They were played up for all they were worth.

It was done in the obstetric field. It was lamented that American mothers paid for maternity with the highest price in life in all the civilized world. Tears were shed over the 16,000 white carnations that would be worn on Mother's Day each year for mothers who died in childbirth. No one questions that public interest and public action resulted, but who does not question the unnecessary fears that were stirred in the hearts of mothers and fathers? It was done to compete with all those equally dramatic campaigns launched on the bewildered public by this agency and that association.

The Planned Parenthood movement, faced with the same conditions, shouted loud and long to be heard in the melée. The emphasis, too, was on the dramatic, the negative. "Birth Control" was the slogan. It was a tremendous job of propagandizing—such a job that, in these days of constructive appeals, people may still be thinking only in terms of the negative, of keeping babies from being born.

All who have been converted to the glorious light of the positive appeal from the darkness of the negative, have a big task ahead to supplant the negative with the positive message; to tell the story that Planned Parenthood can mean just as much in helping husbands and wives who are infertile to have children.

All who have indulged in negative emphases are finding, and will continue to find for a long time to come, the results of past campaigns flying back as Australian boomerangs. Right now I am thinking of those 10 per cent of all married couples who are sterile, many of whom, under the aegis of "Birth Control" teaching, have been needlessly practicing contraception for years. What do you think they're going to say when they learn from the broader and more comprehensive educational efforts that they needed no contraceptive? Their plight reminds me of the tale of Moses Meers:

There was a man who had a clock.  
His name was Moses Meers.  
And every day he wound that clock  
For eight and twenty years.  
Then, one day he found that clock  
An eight-day clock to be.  
A madder man than Moses Meers  
I never hope to see.

We have all matured enough in our thinking after these disillusioning and educating experiences of competition and free-for-all struggle, to work out ways and means of eliminating the weaknesses and dangers of yesteryear. We need today an organic getting-together in thought and philosophy as well as in action. We need to find the common ground upon which we all stand. Just as our democracy is changing and the policy of economic laissez faire is on the way out, so in social progress the policy of laissez faire among those agencies working for human betterment is doomed to extinction.

Now, I am not saying that all our experiences and competitions were not a necessary part of normal growth. I think many of them were. Perhaps we needed an Antediluvian Period, a Caveman Age where the survival of the fittest strengthened and toughened thoughts and tools. Albert Deutsch of the newspaper, P.M., recently lamented the passing of the giants of social reform and the great popular movements which they led, the Jacob Rieses, the Mary Richmonds, the Jane Addamses, the Trudeaus. They were undoubtedly important to social progress. They were important to their day. But really, I do not lament the fact that we have no giants in this year of our Lord 1942. We are beyond the stage of great campaigns for one thing and another. We are coming to the day in our social progress when we must integrate our efforts and our thinking.

The first result of these popular movements of the past was to divide up living and even dying, into segments. We had clinics for this and hospitals for that, associations for one thing, societies for another. Many a maternity patient who received prenatal care in its most literal sense, that is, care that was focused only on her reproductive functions, died from tuberculosis or diabetes or cancer soon after the coming of her baby. Each segment of life was isolated from the other segment and the results on family living were not even considered by the rank and file of organizations and workers.

In the field of obstetrics, for instance, for centuries attention was given to labor and delivery. Only in relatively recent times was the relation of abnormalities and complications of pregnancy associated with difficulties at birth. Then a campaign for prenatal care was launched. But the train of thought could not stop there. The concept of obstetrics was extended to include post-partum care. Doctors and health workers began to realize that the health of the parents before pregnancy, yes, even before marriage, played an important role in safety in childbirth. The health of mothers and fathers depended upon habits and attitudes which led right back to family living. The coming of a baby is not a segment of life, but life itself. It cannot be studied apart from the sum total of living. Thus the movement broadens and generalizes as the years pass.

This is true of every other specialized campaign. I need not trace the development of the charity organization movement into the family welfare movement; or the birth control movement into the planned parenthood movement; or the blossoming of religious thought from the confines of narrow creeds to the expansiveness of the "abundant life," or the growth of the concept of teaching from the three R's to preparation for living.

We are all on common ground, having arrived there through devious paths and strange interludes. The groundwork has been laid for the development of sound, constructive, joint efforts for the preparing of parents to make family life the creative influence it should be in our society.

The whole basis of constructive family living depends upon the knowledge, the spirit, the character of parents and their ability to work out their family salvation with love and understanding.

Today all engaged in human betterment have many questions to think through and answer together. What of the spiritual values of family

life? What of the economic factors, the health factors, the nutrition factors, the hereditary factors in the coming of children? What of the instruction of young people in the construction and function of their own bodies? What of the proper presentation of the conception, growth and birth of a baby in the education of every adolescent? What of the understanding of young married people about abortion, its dangers, about sterility, its causes? What of the freedom of parenthood, freedom to limit families and freedom to have children?

I see small hope of finding answers to these questions, of providing the right kind of education for parenthood, of helping America's parents to make the wisest and best decisions about their family life, when the brand of trust and faith and confidence which we hope to inculcate in tomorrow's young people does not yet exist among the agencies which do the work.

Now I am an optimist. I see the end of overemphasis, of needless and fruitless competition. I see the time coming when all the facts in their right relationships may be presented to the public for clearheaded action. What I am talking about may not be for today, but surely for tomorrow. We have much to learn, all of us. We have to learn to think together, to work together, to do more basic research together in the teaching of the public. We have got to learn to see the relation of our job to the whole picture. Some of the things we do will have to increase; some will have to diminish, some must vanish. We shall have to be able to see our specialized causes put in their relative positions. If we are really sincere about working together, if we are willing to make sacrifices, if our interest is in serving the people and not promoting a particular organization—IF . . . I say, then our efforts to make for sounder, happier, healthier family living in America will be crowned with achievement.

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EDITOR'S NOTE: This paper was read at the recent annual meeting of the Birth Control Federation of America in a symposium on Planned Parenthood. Miss Corbin is the nationally known director of the Maternity Center Association of New York and presents a controversial subject, which now occupies so much public interest, in such a forceful and illuminating fashion, that it deserves the attention of the medical reader. We, therefore, are pleased to publish it in the columns of the JOURNAL.

## Society Transactions

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### CHICAGO GYNECOLOGICAL SOCIETY

*MEETING OF JANUARY 16, 1942*

The following papers were presented:

**Low Cervical Cesarean Section. A Motion Picture in Color.** Charles E. Galloway and Philip H. Smith.

**Some Contributions of Research on Primate Animals to Gynecological Theory.** Carl G. Hartman (by invitation). (For original article, see page 156.)

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### WASHINGTON GYNECOLOGICAL SOCIETY

*MEETING OF NOVEMBER 22, 1941*

**An Evaluation of the Various Types of Cesarean Section.** By Dr. Edward A. Schumann of Philadelphia (by invitation).

**Prolapse of the Uterus During Pregnancy and Labor.** By Dr. Samuel Dodek.

*MEETING OF JANUARY 24, 1942*

The following papers were presented:

**Methods for the Relief of Shock in Obstetrics.** By Dr. Norris Vaux of Philadelphia (by invitation).

**Vesicovaginal Fistula.** By Dr. John Darner.

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### PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

*MEETING OF FEBRUARY 2, 1942*

The following case report was presented:

**Cornual Pregnancy.** By Dr. F. D. Frank.

The following papers were presented:

**Pelvic Pain.** Dr. W. A. Wolf, discussion by Dr. Morris Cohen (by invitation).

**Comparative Maternal Mortality in American Cities With a Population of 500,000 Plus.** By Dr. P. E. Marks (by invitation).

# Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

## Selected Abstracts

### Endometriosis

1. Philipp, E., and Huber, H.: **The Origin of Endometriosis, Including a Contribution to the Pathology of the Interstitial Portion of the Tube**, Zentralbl. f. Gynäk. 63: 7, 1939.
2. Philipp, E., and Huber, H.: **The Clinical Features of Endometriosis in the Light of the Results of Recent Investigation**, Zentralbl. f. Gynäk. 63: 482, 1939.
3. Huber, H.: **Myomata (as related to) Sterility and Fertility With a Further Contribution to the Significance of Tubal Endometriosis**, Zentralbl. f. Gynäk. 63: 760, 1939.
4. Philipp, E., and Huber, H.: **The Extension of Corpus Carcinoma (to the Tube)**, Zentralbl. f. Gynäk. 63: 2153, 1939.
5. Philipp, E., and Huber, H.: **Summary**, Zentralbl. f. Gynäk. 63: 2448, 1939.

This series of studies appears to be of sufficient importance to justify a report at length. Since they make a continuous series and since there is much repetition in each, it is perhaps best to abstract them together.

The first report begins with a brief summary of the various theories of the origin of endometriosis. The major difficulties in the acceptance of these theories as completely satisfactory are detailed and, in particular, attention is called to the failure to transplant menstrual endometrium and to the three well-known cases of endometriosis of the leg and arm. The authors' experiences lead them to the conclusion that the mechanism of transplantation is the most acceptable explanation of etiology. The usual site of implant is evidence in support of this view. They quote what appears to have been the case which directed their attention to the findings which are to be reported. Blood and a portion of endometrium were found free in a Fallopian tube whose interstitial portion was occluded by endometrium.

Endometrium in the Fallopian tube has been described but the actual frequency of its occurrence has not been recognized. The origin of this has been variously ascribed to transplantation (Sampson), redifferentiation (Meyer) and transplantation from a chocolate cyst (Novak). The condition is not to be confused with adenomyosis tubae or salpingitis isthmica nodosa.

In this condition of endometriosis of the tube, it is usual that only the interstitial portion of the tube is involved. The endometrium is continuous with that of the uterine cavity. The lumen of the tube becomes eccentric. Partial or complete closure is produced and the lumen may end in a blind sac. This endometrium undergoes cyclical changes. It may become characteristic of cystic glandular hyperplasia. Squamous epithelial change is occasionally seen. The endometrium may be in the form of a polyp.



Cases are described to illustrate these details. One is of particular interest in relation to what is to follow. A 33-year-old patient was found at operation to have a myoma of the uterus and disseminated endometriosis of the ovaries among other places. The fimbriated ends of both tubes were open but both interstitial portions occluded by endometrium. The remainder of the tube lining was normal.

The remainder of the reports, then, are studies which relate this tubal endometriosis to endometriosis elsewhere, to sterility, to myomas and to some other things.

"The cause of abdominal endometriosis is the above described adenomyosis and endometrial polyps in the tube." "These are not exceptional findings but have a broad importance." Of 23 cases of abdominal endometriosis which were studied, 19 showed endometrial extension to the tube, and of these, 14 showed bilateral tubal involvement. In 9 cases the endometrium was present in the tube in the form of polyps, and in 3 cases the polypoid form was bilateral. In almost all cases the fimbriated ends of the tubes were open but the interstitial portions closed. The importance of this in a consideration of the mechanism of Sampson's retrograde passage of menstrual corpus endometrium is clear.

The authors assume that the passage of endometrium from the interstitial portion of the tube to the abdomen occurs as a result of small pieces being broken off, probably as a result of tubal contraction. Thus, an association with menstruation is not necessary and endometrium may be passed in a state which is known to allow of successful implantation. The authors believe that other types of transplantation may occur but that these are rare.

One other finding is presented in support of the hypothesis. In the presence of closure of the abdominal ostia, the whole tube may become lined by endometrium. Three such cases are described and it is stated that no such cases are described in the presence of open ostia.

It is further stated that the site of implantation in the pelvis has to do with the concentration of estrin. It is assumed that the nearer the ovary, the greater the estrin concentration.

Endometriosis of the umbilicus, inguinal region and metastatic forms are still explained in the conventional manner.

In summary, then, the authors state that endometriosis arises by

1. Direct extension from the uterus, as that in the abdominal wall, parametrium, retroperitoneal connective tissue, vagina, etc.
2. Much more often (a) passage from broken off bits of endometrium from the interstitial portion of the tube which then implant (4/5 of authors' cases); and (b) less often than 2a, by passage and implantation of viable endometrium broken off by intrauterine procedures.
3. Occasional hematogenous passage.

In the second report, consideration is first given to terminology and classification. Endometriosis is defined as a condition which is characterized by the presence of uterine mucosa in areas where it does not belong. They suggest that the term adenomyosis be dropped. There is no significance in the term endometrioid since the tissue is real endometrium and not only something similar to it.

The following terminology and classification are recommended:

1. Endometriosis which is continuous with the endometrium corporis—primary (localized) endometriosis.
  - (a) Endometriosis of the uterine musculature (endometriosis interna)
  - (b) Endometriosis which has spread from 1a to the parametrium, retroperitoneal connective tissue, bladder, abdominal wall scars, etc.
  - (c) Endometriosis which has spread to the tube and is continuous with the endometrium of the uterine cavity.

2. Endometriosis without direct continuity with the endometrium corporis—secondary endometriosis.

(a) Intraperitoneal spread to the ovary, uterus, peritoneum, cul-de-sac, etc.

(b) Extraperitoneal spread to

(1) region of the uterus as the vagina to the inguinal region and the umbilicus, etc.

(2) distant from the uterus as extremities and (?) lungs.

A list of the frequency of involvement of various sites is given. Conditions necessary for growth and the relation of these to site, function, and age of origin are discussed. They limit its clinical appearance to the ages of sexual activity. The age distribution and average age of the authors' patients show the condition to be one of advancing age in terms of sexual activity which suggests that disturbances of ovarian function and hormonal stimulation of the uterus and its mucosa may play a part in giving rise to it.

The peculiar histolytic power of the stroma of endometriosis is discussed together with the morphologic differentiation of the usual benign and the rare malignant form. An interesting case is described in which histologic control with a time interval showed the development of a sarcoma from a benign endometriosis.

The third report deals with the relationship between the occurrence of myomas and tubal endometriosis and their effect in interference with fertility. It is pointed out that the presence of myomas tends to sterility. The mechanism of this has never been satisfactorily explained.

The first part of the paper is given over to a statistical study of the myoma-fertility relationships. As a standard for normals the figures supplied from the German census and contained in the *German Year Book* reports for women married between 1907 and 1925 is used. Those years are chosen to make the material comparable in time to the experiences of his patients. The reports are based on 10,500,000 women. For comparison with these he has 480 married women with myomas.

A great many interesting figures are given. The interested reader is referred to the text for these tables.

He concludes: (1) There is no evidence of a special predisposition in the unmarried to the development of myomas. (2) The relative fertility of women who develop myomas is decreased. (3) The last pregnancy in the myomatous woman occurs four years earlier than in the average. (4) There is no real primary sterility in the woman who develops myomas. If she marries early enough, she can conceive. She shows what appears to be a primary sterility when she marries at an age when the myoma patient is developing her secondary sterility. (5) Multiple myomas are associated with a much greater decrease in fertility and increase in sterility than the solitary myoma. (6) The patient with myomas tends to become sterile at 26 to 29 years of age. (7) The myoma shows its effect on fertility and in the production of sterility almost at the time of its origin or at least early in its development. Its major effect then is not to be explained by simple mechanics alone.

The reader will wonder what this has to do with endometriosis. The second or histologic portion of this report goes on to show that in his series, half of all the myomas investigated showed an associated tubal endometriosis as has been described above. Most of these produce complete closure of the interstitial portion of the tube. Sterility always follows this and frequently follows the incomplete closure. Ten cases are detailed. Of the whole myoma group, 54.9 per cent had an associated tubal endometriosis. This was present in 33 per cent of the solitary and 69.6 per cent of the multiple myomas. Conversely, of 73 myomas without tubal endometriosis, 29 of the cases were multiple myomas, and 44 were solitary. There is no satisfactory explanation for the association of myomas and tubal endometriosis.

This finding is of significance in the therapy of sterility in the presence of myomas. The author reports 42 conservatively operated myomas in married women in active sex life. Of these only 8 subsequently became pregnant.

The tubal closure can be demonstrated by hysterosalpingography. Excluding premenstrual closure and closure by submucous myomas, all closure of the interstitial portion of the tube is due to endometriosis. This is confirmed when, in the absence of filling of the tube, the uterine shadow ends in a peak or button shape. The details of the evaluation of the x-ray findings will be reported later.

The clinical significance is obvious.

The fourth report deals with the effect of tubal endometriosis in allowing extension of corpus carcinoma. Sixty-two cases of corpus carcinoma were studied. Endometriosis of the interstitial portion of the tube at least was found bilaterally in 16 and unilaterally in 13 cases. Of these 62 cases, the carcinoma had extended to the interstitial portion of the tube in 16. In 8 of these, the remains of a primary endometriosis were found, while in the other 8, carcinoma alone was present. Eight cases are detailed.

The significance of this in attempts at treatment of corpus carcinoma by means of intrauterine radium alone is clear. It may also explain some recurrences where the surgical attack has not included removal of the tubes.

The fifth report is a short summary.

This work is an interesting and perhaps important contribution. While the originals contain much repetition and too much speculation, they should certainly be carefully read. The work would seem to justify confirmatory studies.

J. L. McKELVEY.

**Philipp and Huber: New Aspects of Pathogenesis of Endometriosis, Deutsche med. Wehnschr. 66: 1242, 1940.**

According to Philipp and Huber endometriosis develops either by continuous proliferation of the uterine mucosa or more frequently by implantation. In the majority of cases of abdominal endometriosis the origin of the implantation is the endometriosis of the interstitial portion of the tube; in the others the source is the uterine mucosa itself. The implantations of abdominal endometriosis make their way through the tube or they may utilize other available routes. Hematogenic spreading is theoretically possible. The authors on the basis of their investigations arrive at a unitary interpretation of endometriosis. They reject the theory of serosa epithelium in its original and modified form, as well as the assumption that every mesenchyma is capable of forming foci of endometriosis. They believe that local formation of foci of endometriosis as the result of tissue differentiation is no longer tenable. Their own conception is similar to that of Sampson, who was first to recognize implantation of detached fragments of uterine mucosa as the cause of endometriosis. Sampson's theory met opposition, because it erroneously presupposed that cast-off menstrual mucosa was the source. It is the living freshly built-up mucosa which is disseminated. The prerequisites in the majority of cases are the existence of endometriosis in the interstitial portion of the tube and a functioning ovary. Endometriosis does not develop before or after the period of ovarian function, except, perhaps, when ovarian hormones are administered. The importance of hormones in the development of implantation is demonstrated by the fact that they are frequently localized near the ovaries. A favorite location is the ovary itself, where so-called chocolate cysts develop. The authors were able to observe such cysts in various stages of development. They emphasize that endometriosis owes its development to the special properties of the uterine mucosa; the capacity of the cytogenic stroma to grow into deeper layers and the ability of uterine mucosa

to attach itself when carried outside the uterus. The route of spread plays a minor role, dissemination taking place most frequently by way of tubes into the abdominal cavity. Possibility of hematogenic dissemination has been established by microscopic studies. Perfusion of the tissues with ovarian hormones produces more favorable conditions for implantation.

J. P. GREENHILL.

**Rintelen, P. W.: Incidence of Tubal Endometriosis in Women With Seemingly Healthy Genitalia, Zentralbl. f. Gynäk. 64: 1042, 1940.**

Rintelen studied microscopically sections of tubes of 513 women who were sterilized for various reasons. In none of them either from the history or at the time of operation had an endometriosis been suspected.

However, he discovered in 130 patients, aged between 13 and 20, 6 instances of endometriosis; in 213, aged between 21 and 30, 9 instances; in 154, aged between 31 and 40, 6 cases of endometriosis; but none in 16 patients, aged between 41 and 45.

Thus there were 21 instances of tubal endometriosis discovered in this series of apparently healthy women, an incidence of 4 per cent.

In those sections in which curettage material was mounted together with the tubal tissue, the ectopic endometrium was found to be in the same phase of cyclic activity as the true endometrium.

R. J. WEISSMAN.

**Turunen, Aarno: Clinic on Endometriosis Externa, Acta obst. et gynec. Scandinav. 19: 477, 1939.**

A group of 200 cases of endometriosis externa treated at the University Women's Clinic in Helsinki is reported. Five of these patients were treated by irradiation and 195 by laparotomy. Large endometriotic hematomas in the ovaries were met with in about 43 per cent of the cases.

Dysmenorrhea, considered to be the severest symptom, was present in 72 per cent of the cases. Rectal symptoms were observed in 46 per cent, and symptoms from the urinary bladder in 7.2 per cent of the cases. The periodicity of these symptoms was not always conspicuous. Menorrhagia and metrorrhagia were produced only by far-advanced endometriosis externa. Of the married women 90 per cent were sterile, primary sterility being present in 43.6 per cent and secondary sterility in 46.4 per cent of the cases. The correct diagnosis was made before the operation in 50 per cent of the cases.

Radical operations were performed in 43 and conservative operations in 152 cases. It was possible to preserve the capability of conception in 124 patients (63.5 per cent). The mortality rate for the operations was 0.52 per cent. Of the previously sterile women 26 (31.7 per cent) became pregnant after the operation.

J. P. GREENHILL.

**Meigs, Joe Vincent: Endometriosis—Its Significance, Ann. Surg. 114: 866, 1941.**

The author feels that Iwanoff and Meyer's theory of metaplasia of the coelomic epithelium with the production of endometrium is the correct theory. Clinic patients show less endometriosis than patients in private practice, because the former are of a social status that marries early and has children frequently. Twenty-eight per cent of the author's private abdominal operations (gynecologic) showed endometriosis as against 5.8 per cent in the Massachusetts General Hospital group. The



significance of endometriosis is that it is a stigma of infertility, and it is due to uninterrupted menstrual cycles, because of late marriage and infrequent child-bearing.

**Wespi, J. H., and Kletzhandler, M.: Scar Endometriosis, Monatschr. f. Geburtsh. u. Gynäk. 111: 169, 1940.**

During the years 1923 to 1939, the authors observed a total of 73 cases of endometriosis in laparotomy scars. This is astonishing when we consider that only 390 similar cases have been reported in the world literature. In five of the 73 cases, a cesarean section had been performed, but in the 68 other cases, pregnancy had been interrupted by an abdominal operation. In 76 per cent of the cases, the endometriosis was located at one corner of the abdominal wound whereas in only 20 per cent it was situated in the middle. (In 4 cases, there was no note as to the location.)

The cause of the endometriosis in the authors' cases was implantation of decidua from the uterine cavity to the abdominal wound. This explanation holds true both for the early abdominal hysterotomy cases and the cesarean sections. The reason that only 5 cesarean sections were encountered as opposed to so many abdominal hysterotomy cases is that the decidua at term possesses very little tendency to grow. Furthermore a curette was not used in the cesarean sections but was employed in the other cases.

By changing the technique of their operations in such a way that no endometrium could come in contact with the abdominal wound, the authors have been able to reduce the frequency of scar endometriosis from 3.4 per cent to 0.9 per cent.

Among the 390 cases of scar endometriosis reported in the literature, the chief types of operations which preceded the endometriosis were as follows: ventrofixation, 113; cesarean sections, 41; hysterotomy, 49; other openings made in the uterus, 26; adnexal operations, 51; appendectomy, 18; and removal of vulvar vaginal and perineal scars, 43.

J. P. GREENHILL.

**Von Torzsay-Kiss: Endometriosis of Cervical Origin, Zentralbl. f. Gynäk. 64: 2257, 1940.**

It was long ago shown by Robert Meyer that heterotopic growths may arise which have their origin in the glands of the cervix. J. von Torzsay-Kiss reports a few such cases. Endometriosis arising in the cervix differs from endometriosis which has its origin in the corpus endometrium, both histologically and functionally. In corporal endometriosis the glands are lined by single-celled cylindric cells with their nuclei in the center of the cells. In cervical endometriosis, the glands are likewise lined by single-celled cylindric cells, but the nuclei are typically in the basal portion of the cells. Functionally, endometriosis of corporal origin is under the influence of the ovarian hormones, and it therefore exhibits the physiologic changes. On the other hand, in endometriosis arising in the cervix the cells have only a secretory function and secrete a mucous discharge identical with that observed in the cervix. Hence, not all endometriotic growths respond to ovarian activity. The author therefore suggests that endometriosis be classified as corporal or cervical, depending on the origin. He believes cervical endometriosis does not result from transformation of cells in situ but is due to implantation of pieces of cervical mucosa. There is ample occasion for such implantations when one considers the frequency of trauma to the cervix.

J. P. GREENHILL.



**Portes and Varangot:** *Endometriosis and Pregnancy*, Gynéc. et obst. 40: 298, 1940.

Endometriosis in the presence of pregnancy is rare, particularly because of the high incidence of sterility in women with endometriosis, and because this condition is found chiefly in women in the fifth decade of life when conception is uncommon. Portes and Varangot report a case of endometriosis occurring during pregnancy. A biopsy performed late in pregnancy led to the wrong diagnosis of spinal cell carcinoma and a cesarean section was performed. After operation, the tissue was found to be endometriosis and not cancer. The error was due to the change which took place in the cells of the tumor because of the gestation.

A review of the literature revealed that endometriosis during pregnancy may lead to errors in diagnosis and may be the cause of serious complications. During pregnancy there are two sites of predilection for endometriosis: the uterus, and the rectovaginal septum. Often uterine endometriosis is mistaken for a fibroid. Uterine endometriosis may lead to rupture of the uterus and severe hemorrhage during delivery. Rectovaginal endometriosis may produce dystocia and necessitate a cesarean section.

De Jong and de Snoo maintain that most so-called ectopic decidual nodules which are frequently observed on the peritoneum, in the ovary and in lymphatic glands are foci of endometriosis which have undergone degenerative changes during pregnancy.

J. P. GREENHILL.

**Levi, Alexander A.:** *Pedunculated Endometrial Cyst of the Uterus*, New England J. Med. 224: 156, 1941.

The case is reported of a 39-year-old woman in whom the following gynecologic anomalies were present at the same time: a pedunculated endometrial cyst within the uterine cavity, an intramural fibroid, and a dermoid cyst of the left ovary.

After several severe uterine hemorrhages, the cervix was dilated and a bluish globular mass, about 3.5 cm. in diameter, removed. Histologic study proved it to be an unusually large endometriosis cyst, its wall consisting of endometrium and some atrophic myometrium. Pedunculated endometrial cysts are extremely rare.

HUGO EHRENFEST.

**Bazy, Blondin and Chene:** *Clinical and Practical Significance of Rectal Endometrioma*, Presse méd. 47: 785, 1939.

The authors report 2 cases of rectal endometrioma, each proved by biopsy. They draw attention to the symptomatology of these cases, a painfully acute to subacute abdomen in the premenstrual period, usually afebrile and associated with diarrhea in which mucus and blood are prominent. There may be isolated cases with premenstrual rectal hemorrhage. Other patients complain of a premenstrual pain which bears no relationship to defecation.

By means of proctoscopic examination in the premenstrual period, these small tumors are usually easily recognized but are difficult to see postmenstrually. The writers suggest a functional test by the use of folliculin hormone prior to rectal examinations in patients complaining only of a rectal neuralgia.

One patient, aged 44 years, had been treated for hemorrhoids four years before. A proctoscopic examination revealed a tumor 7 cm. on the anterior surface of the ampulla. Her natural menopause resulted in complete relief.

The second woman, aged 45 years, had a painful abdomen premenstrually for each of the preceding eighteen months. This was accompanied by an afebrile course and a bloody diarrhea. A rectal examination revealed a budlike tumor 12 cm. on the anterior ampullar wall. X-ray castration gave complete relief.

CLAIR E. FOLSOME.

**Blaikley, J. B.: Endometrioma of the Colon Causing Stricture, Proc. Roy. Soc. Med. 34: 810, 1941.**

The author describes a specimen obtained by operation, representing a stricture so small that not even the tip of the little finger could be passed. The covering mucous membrane was freely movable over the fibrous tissue as hard as a cartilage. Microscopic examination showed here and there typical islets of endometrium in the fibrous tissue.

The patient was a single woman, 40 years old, who always had a dysmenorrhea with pain in the left iliac fossa, which gradually got worse. During every menstrual period she had severe, colicky pain and was constipated. Gynecologic examination showed a slightly enlarged uterus and a tender nodule on the back of it. In the middle of the pelvic loop of the colon was found a small mass with thickened walls. It was removed after completion of a subtotal hysterectomy with bilateral oophorectomy. As a rule, in cases of endometriosis, isolated masses cause only a local puckering of the intestinal wall; complete encirclement undoubtedly must be rare.

HUGO EHRENFEST.

**Tasch, H.: Fibroma Ovarii With Endometriosis and Ascites, Zentrabl. f. Gynäk. 64: 1823, 1940.**

The author presents an interesting case of an ovarian fibroma, weighing 3 kilograms, in a 60-year-old woman. On opening the abdomen approximately 10 liters of serous fluid were released. Histologic studies showed the presence of endometrial tissue with cystic glandular hyperplasia. Although ovarian fibroma and ascitic fluid are not uncommon, the author was unable to find reports of endometriosis within a fibroma.

R. J. WEISSMAN.

### Myoma

**Grosbeck, W., and Pool, R. M.: Similar Fibroid Tumors Occurring in Identical Twins, South. M. J. 33: 1090, 1940.**

A paper of McFarland and Meade published in 1932 stimulated interest in this unusual condition. In it they stated that tumors arising in one twin of an identical pair must occur similarly, simultaneously and symmetrically in the mate. The authors feel that their brief case report represents a contribution to the literature on the subject, since they were unable to find a single record of a similar condition.

The patients considered in this paper were colored, 24-year-old identical twin sisters. In all their physical characteristics and mannerisms there was a remarkable similarity. One of them had noticed enlargement of the lower abdomen for two years. Upon admission she complained of pain in that region, and stated that she had been nauseated and vomiting for several days. Menses were irregular and profuse. Her uterus was enlarged by multiple fibroid tumors, and it extended above the umbilicus. The twin sister had been aware of a prominence of the lower abdomen for only a month; there was some frequency of urination and dysuria of one week's duration. Nodular distortion of the uterus by fibroid tumors brought the tumefaction to the level of the umbilicus. Both patients had a supravaginal hysterectomy, and they made uneventful recoveries. Their anesthesia charts showed a similarity in pulse rate, systolic and diastolic pressures. The histologic diagnosis was simple multiple leiomyomas with considerable myxomatous degeneration in one of the tumors.

This report includes a comprehensive bibliography.

ARNOLD GOLDBERGER.

Hüssy, P.: **Malignant Myoma**, Zentralbl. f. Gynäk. 64: 1540, 1940.

The author reports a case in which a histologically benign tumor metastasized in a manner typical of frankly malignant growths. An obese 42-year-old para v consulted a physician for fever and precordial pain. An enlarged heart with incompetent pulmonary valve was found. Radiographs revealed peculiar lung shadows. An abdominal tumor was palpable, apparently deriving from the right ovary and a diagnosis of ovarian carcinoma with pulmonary metastases was made. At operation a myoma of over 1 kilogram weight was found attached to the uterus. A supra-vaginal hysterectomy was done. The patient died a cardiac death a few hours later. The metastatic nodules in the lungs showed a benign structure exactly similar to that of the uterine tumor. Small nodules were found on the leaflets of the tricuspid valve and in both lower branches of the pulmonary artery. The author emphasizes that histologic benignancy does not always signify an absence of clinical malignancy.

R. J. WEISSMAN.

Cirio, C. R.: **Myometrectomy. A New Technic for the Treatment of Uterine Fibroids**, Presse méd. No. 48, p. 925, 1940.

The author describes a new operative technique for the removal of fibroids from the uterus. The operation, developed in his Buenos Aires clinic, is termed myometrectomy. The tubes and the round ligaments are severed at the cornual regions of the fundus uteri. Approximately one-half of the superior mass of the fundus uteri and its accompanying tumor, if present, is excised by transverse incisions. This portion of the operation resembles the defundation technique.

The writer then proceeds to enucleate, between the uterine serosa and the endometrium, the residual portion of the fibroids and any excessive myometrium in the remaining segment of the uterus. Care is taken to preserve the residual endometrium in this lower segment. The upper ends of the endometrium are then coapted with suture. The mesial ends of the Fallopian tubes and the round ligaments are buried in the new cornual regions while the remaining superior edges of the myometrium are approximated into a new fundus-like extremity. Peritonization of the serosal surfaces concludes the operation.

Cirio has performed this operation upon forty different patients. He notes that Ribarro, of Rio de Janeiro, has done nine similar operations. The writer concludes that his operation is of value in that it tends to remain a conservative procedure and coincidentally permits recurrence of normal cyclic function. The article is well illustrated with six halftone plates.

CLAIR E. FOLSOME.

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## Correspondence

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### Bibliography of Brenner Tumor

#### To the Editor:

In the June, 1942, issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, page 984, the cytologic details of the Walthard rest and the Brenner tumor were described. Since publication of this article a paper by Varangot (Les Tumeurs Ovariennes du Type Brenner. Etude Anatomique, Gynéc. et obst. 38: 11, 1938) has come to my attention. In this communication findings similar to those described by me are recorded. This paper appears generally to have escaped notice, and it is with pleasure that I acknowledge this original reference to the nucleus which I have described as a fundamental characteristic of the Brenner tumor.

622 WEST 168TH STREET  
NEW YORK, N. Y.  
JUNE 12, 1942

D. N. DANFORTH, M.D.

## ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES\*

(Appears in January, April, July, October)

- American Gynecological Society.** *President*, George W. Kosmak, New York, N. Y. *Secretary*, H. C. Taylor, Jr., 830 Park Ave., New York, N. Y. Annual meeting, May, 1943.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** *President*, W. R. Cooke, Galveston, Texas. *Secretary*, James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting, White Sulphur Springs, Va., September 9-11, 1942.
- Central Association of Obstetricians and Gynecologists.** *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Iowa City, Iowa. Next meeting, Des Moines, Ia., October, 1942.
- South Atlantic Association of Obstetricians and Gynecologists.** *President*, Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Next meeting, February, 1943, Southern Pines, N. C.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, L. E. Phaneuf. *Secretary*, Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June, 1942, Atlantic City, N. J.
- New York Obstetrical Society.** *President*, Henry T. Burns, *Secretary*, Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** *President*, John C. Hirst. *Secretary*, James P. Lewis, 3815 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** *President*, Edward Allen. *Secretary*, Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** *President*, Bruce A. Harris. *Secretary*, John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** *President*, Lawrence Warton. *Secretary-Treasurer*, John W. Haws, 9 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.
- Cincinnati Obstetrical Society.** *President*, E. W. Enz. *Secretary*, Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Howard Stearns. *Secretary*, William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** *President*, Thomas Evans, Jr. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** *President*, Thos. Almy, Fall River, Mass. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** *President*, Frederick L. Good. *Secretary*, R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** *President*, T. Floyd Bell. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, San Francisco, Calif., November, 1942.

\*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.



- Washington Gynecological Society.** *President*, John Warner. *Secretary*, L. L. Cockerille, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.
- New Orleans Obstetrical and Gynecological Society.** *President*, E. L. Zander. *Secretary*, Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** *President*, T. Henshaw Kelly. *Secretary*, R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** *President*, Roy Grogan. *Secretary*, J. McIver, 714 Medical Arts Building, Dallas, Texas.
- Michigan Society of Obstetricians and Gynecologists** (formerly the Detroit Obstetrical and Gynecological Society). *President*, H. C. Walser. *Secretary*, Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** *President*, Glen A. Wood. *Secretary*, Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** *President*, T. M. Boulware, Birmingham, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala. Next meeting Montgomery, Ala., April, 1942.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** *President*, Glen N. Rotten. *Secretary*, R. Philip Smith, 1305 Fourth Avenue. Meetings third Wednesday.
- Denver Obstetrical and Gynecological Society.** *Secretary*, Emmett A. Meehler, 1612 Tremont St., Denver, Colo.
- Wisconsin Society of Obstetrics and Gynecology.** *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

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### Erratum

Throughout the article by Paul C. Roberts entitled "Intravenous Administration of Basergen During the Third Stage of Labor," p. 849, of the May issue of the JOURNAL, the word Basergen should be Basergin.